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JOB STRAIN AS A RISK FACTOR FOR OBESITY, PHYSICAL INACTIVITY AND TYPE 2 DIABETES – A MULTI-COHORT STUDY

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ACADEMIC DISSERTATION

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TIIVISTELMÄ

Työstressi on yleinen vaiva työssäkäyvillä. Euroopan Unionin tietojen mukaan noin viidennes työntekijöistä ilmoittaa kokevansa työstressiä, mutta arviot yleisyydestä vaihtelevat määritelmästä ja tutkimuksesta riippuen 5% ja 80% välillä. Eniten tutkitun työstressimallin mukaan työstressi ilmenee tilanteessa, jossa työn vaatimukset ovat suuret ja työn hallinta vähäistä. Tällaisen stressin arvellaan voivan heikentää elämänlaatua ja olevan yhteydessä useisiin haitallisiin terveysvaikutuksiin. Varsinainen tutkimustieto aiheesta perustuu kuitenkin usein pieniin aineistoihin sekä ristiriitaisiin lopputuloksiin. Tämän työn tavoitteena oli tutkia työstressin yhteyttä diabetekseen sekä sen riskitekijöihin, erityisesti lihavuuteen sekä fyysiseen passiivisuuteen.

Tutkimuksessa käytetään laajaa IPD-Work-konsortion tutkimusaineistoa. Tämä tutkimuskonsortio on perustettu tuottamaan tietoa työperäisten psykososiaalisten kuormitustekijöiden yhteyksistä erilaisiin terveysvasteisiin, kuten kroonisiin tauteihin, mielenterveyden häiriöihin, työkyvyttömyyteen sekä kuolleisuuteen. Konsortiossa on mukana useita erilaisia tutkimuskohortteja eri maista.

Tässä väitöskirjatyössä analysoidaan 19 tutkimuskohorttia. Tulokset perustuvat aiheesta riippuen noin 47 000-170 000 tutkittavaan työntekijään. Työstressiä sekä elintapoja kuvaavat tiedot on saatu osallistujan lähtötilanteessa täyttämistä kyselylomakkeista. Joissakin tarkasteluissa on käytetty myös muutamaa vuotta myöhemmin kysyttyjä seurantatietoja työstressin ja elintapojen muutoksien mittaamiseksi. Biologiset riskitekijät, kuten verenpaine sekä kolesteroli, on mitattu osassa tutkimuskohorteista alkutilanteen terveystarkastuksessa. Diabetekseen sairastuminen on määritetty kohortista riippuen rekisteritietojen, seurantakyselyjen tai toistettujen terveysmittauksien perustella. Kaikki muuttujat on harmonisoitu ennen analyysien suorittamista ja vastemuuttujiin yhdistämistä.

Analyysimenetelminä käytettiin Pearsonin korrelaatiokertoimen, sensitiivisyyden, spesifisyyden sekä Kappakertoimen laskemista, sekä yksilötason yksi- ja kaksivaiheista meta-analyysiä. Kaksivaiheisen meta-analyysin tapauksessa riskiestimaatit keskivirheineen laskettiin ensin logistista regressiota käyttäen. Myös sekamalleja ja Coxin regressiota hyödynnettiin aineiston analysoimisessa.

Kaikissa tutkimuskohorteissa ei ollut käytetty alkuperäistä, standardoitua mittaria työstressin määritykseen. Tästä johtuen työ aloitettiin vertaamalla näitä osittaisia skaaloja alkuperäisillä mitattuihin. Tuloksena havaittiin suuri yhdenmukaisuus osittaisten sekä alkuperäisten mittareiden välillä (sensitiivisyys >0.43, spesifisyys >0.93, Kappa > 0.54). Havaittiin myös, että työstressin määritys oli riittävä, vaikka osa kysymyksistä puuttui. Täten jatkoanalyysien kannalta osittaisten mittarien käyttö todettiin hyväksyttäväksi.

Seuraavissa analyyseissä havaittiin työstressin olevan yhteydessä sekä diabetekseen että sen riskitekijöihin, erityisesti elintapamuuttujiin. Voimakkaimmat yhteydet havaittiin lihavuuden, fyysisen passiivisuuden ja diabeteksen suhteen. Iällä ja sukupuolella vakioidussa mallissa riski kokea työstressiä oli 1.19 (95% luottamusväli 1.13-1.25) ja 1.30 (95% lv 1.16-1.46) – kertainen lihavuuden kategorioissa normaalipainoisiin verrattuna. Työstressi oli myös yhteydessä liikunnalliseen passiivisuuteen (iällä ja sukupuolella vakioitu vaarasuhde 1.36, 95% lv 1.25-1.48). Diabetes oli yleisempää työstressistä kärsivien keskuudessa (vaarasuhde 1.33, 95% lv 1.13-1.56). Lisäksi diabetekseen sairastui seurannan aikana useammin ne, joilla oli työstressiä lähtötilanteessa. Vaarasuhde työstressiä kokevien ja muiden työntekijöiden välillä oli 1.15 (95% luottamusväli 1.06–1.25) kun ikä-, sukupuoli- ja sosioekonomiset erot oli otettu huomioon. Tämä yhteys ilmeni ylipainoisilla, fyysisesti passiivisilla, tupakoijilla ja alkoholia runsaasti käyttävillä sekä niillä, joilla ei ollut näitä riskitekijöitä. Työstressin ei havaittu olevan yhteydessä verenpaineeseen ja kolesteroliarvoihin.

Yhteenvetona voidaan todeta, että havaitut yhteydet työstressin ja diabeteksen, lihavuuden, fyysisen passiivisuuden välillä olivat tilastollisesti merkitseviä, mutta heikkoja. Näiden tulosten perusteella työstressiä vähentävien interventioiden vaikutus diabeteksen ilmaantuvuuteen jäisi väestötasolla vaatimattomaksi, mutta asian varmistamiseen tarvitaan interventioon perustuvia lisätutkimuksia.

ABSTRACT

Work is a common source of stress in modern societies. There are various definitions of work stress, but job strain is the most widely used concept referring to a condition in which an employee has simultaneously high psychological job demands and a low level of work control. The aim of the study reported in this thesis was to examine the extent to which work stress might increase the risk of incident type 2 diabetes, and its association with major diabetes risk factors such as obesity and physical inactivity.

Data were obtained from the cohort studies participating in the IPD Work Consortium, a collaborative research effort set up to examine the associations between work-related psychosocial factors and disease outcomes. The Consortium originally consisted of 17 European cohort studies, but new ones have been added. The total number of studies included in the analyses discussed in this thesis is 19, and the population samples range from 47,000 to 170,000 adults depending on the availability of relevant data. Job strain and lifestyle factors, including weight and height, were assessed by questionnaire at the study baseline, repeated at follow-up in six of the 19 studies. Biological risk factors including weight, height, blood pressure and blood lipids were measured in a medical examination in eight of the studies. Incident type 2 diabetes was ascertained from health and mortality registers (11 studies), annual questionnaires (1 study) or repeated glucose-tolerance tests during the follow-up (1 study). Operationalized definitions of job strain, lifestyle and covariate variables were harmonised before any analysis of the associations or linkage to outcome data. Harmonisation of the variables was tested using Pearson correlation coefficients, sensitivity, specificity, and Kappa statistics. Associations with incident type 2 diabetes and its risk factors were examined in one- and two-stage meta-analyses of individual participant data. Two-stage meta-analyses were conducted in which the study-specific effect estimates and their standard errors were first obtained using logistic regression or Cox proportional hazards regression, then the estimates were pooled using random-effects meta-analysis.

Harmonisation analyses were conducted to compare the agreement between alternative operationalizations of the job-strain variable, and partial scales were developed that were comparable to the complete scales. Good or at least adequate agreement between the harmonised and the full job-strain measure (sensitivity >0.43, specificity >0.93, Kappa >0.54) justified further pooled

analyses. Job strain was associated with diabetes and its risk factors. After adjustment for age and sex, the odds ratio of having job strain was 1.19 (95% CI 1.13-1.25) times higher for class-I obese participants (BMI 30 to <35km/m^2), and 1.30 (95% CI 1.16-1.46) times higher for the combined class Ⅱ and Ⅲ obesity groups (BMI at least 35 kg/m^2), compared to normal-weight participants (BMI 18.5 to <25 kg/m^2). Job strain was also associated with physical inactivity (age and sex adjusted odds ratio 1.36, 95% CI 1.25-1.48). The risk of incident diabetes during a mean follow-up of 10.3 years was 1.15 (95% CI 1.06-1.25) times higher among the participants who reported job strain than among those who did not. This association was also observed in the subgroups, including those with and without lifestyle risk factors, and before and after adjustment for lifestyle factors including obesity and physical inactivity. According to cross-sectional analysis adjusted for age, sex and socioeconomic position, the odds for diabetes were 1.33 (95% CI 1.13-1.56) higher among participants with job strain as opposed to those without.

In conclusion, these findings show a robust association between job strain, diabetes and its key risk factors. Nonetheless, the effect size was modest, suggesting that interventions to reduce job strain would not be very effective in combating diabetes on the population level.

LIST OF ORIGINAL PUBLICATIONS

The thesis is based on the following original publications, which are referred to in the text by their Roman numerals. The articles are open access and reprinted with the permission of the copyright holders.

I Fransson EI, Nyberg ST, Heikkilä K, Alfredsson L, Bacquer de D, Batty GD, Bonenfant S, Casini A, Clays E, Goldberg M, Kittel F, Koskenvuo M, Knutsson A, Leineweber C, Magnusson Hanson LL, Nordin M, Singh-Manoux A, Suominen S, Vahtera J, Westerholm P, Westerlund H, Zins M, Theorell T, Kivimäki M. Comparison of alternative versions of the job demand-control scales in 17 European cohort studies: the IPD-Work consortium. *BMC Public Health*. 2012 Jan 20;12:62.

II Nyberg ST, Heikkilä K, Fransson EI, Alfredsson L, De Bacquer D, Bjorner JB, Bonenfant S, Borritz M, Burr H, Casini A, Clays E, Dragano N, Erbel R, Geuskens GA, Goldberg M, Hooftman WE, Houtman IL, Jöckel KH, Kittel F, Knutsson A, Koskenvuo M, Leineweber C, Lunau T, Madsen IE, Hanson LL, Marmot MG, Nielsen ML, Nordin M, Oksanen T, Pentti J, Rugulies R, Siegrist J, Suominen S, Vahtera J, Virtanen M, Westerholm P, Westerlund H, Zins M, Ferrie JE, Theorell T, Steptoe A, Hamer M, Singh-Manoux A, Batty GD, Kivimäki M; IPD-Work Consortium. Job strain in relation to body mass index: pooled analysis of 160 000 adults from 13 cohort studies. *J Intern Med*. 2012 Jul;272(1):65-73.

III Fransson EI, Heikkilä K, Nyberg ST, Zins M, Westerlund H, Westerholm P, Väänänen A, Virtanen M, Vahtera J, Theorell T, Suominen S, Singh-Manoux A, Siegrist J, Sabia S, Rugulies R, Pentti J, Oksanen T, Nordin M, Nielsen ML, Marmot MG, Magnusson Hanson LL, Madsen IE, Lunau T, Leineweber C, Kumari M, Kouvonen A, Koskinen A, Koskenvuo M, Knutsson A, Kittel F, Jöckel KH, Joensuu M, Houtman IL, Hooftman WE, Goldberg M, Geuskens GA, Ferrie JE, Erbel R, Dragano N, De Bacquer D, Clays E, Casini A, Burr H, Borritz M, Bonenfant S, Bjorner JB, Alfredsson L, Hamer M, Batty GD, Kivimäki M. Job

strain as a risk factor for leisure-time physical inactivity: an individual-participant meta-analysis of up to 170,000 men and women: the IPD-Work Consortium. *Am J Epidemiol*. 2012 Dec 15;176(12):1078-89.

IV Nyberg ST, Fransson EI, Heikkilä K, Alfredsson L, Casini A, Clays E, De Bacquer D, Dragano N, Erbel R, Ferrie JE, Hamer M, Jöckel KH, Kittel F, Knutsson A, Ladwig KH, Lunau T, Marmot MG, Nordin M, Rugulies R, Siegrist J, Steptoe A, Westerholm PJ, Westerlund H, Theorell T, Brunner EJ, Singh-Manoux A, Batty GD, Kivimäki M; IPD-Work Consortium. Job strain and cardiovascular disease risk factors: meta-analysis of individual-participant data from 47,000 men and women. *PLoS ONE*. 2013 Jun 20;8(6):e67323.

V Nyberg ST, Fransson EI, Heikkilä K, Ahola K, Alfredsson L, Bjorner JB, Borritz M, Burr H, Dragano N, Goldberg M, Hamer M, Jokela M, Knutsson A, Koskenvuo M, Koskinen A, Kouvonen A, Leineweber C, Madsen IE, Magnusson Hanson LL, Marmot MG, Nielsen ML, Nordin M, Oksanen T, Pejtersen JH, Pentti J, Rugulies R, Salo P, Siegrist J, Steptoe A, Suominen S, Theorell T, Väänänen A, Vahtera J, Virtanen M, Westerholm PJ, Westerlund H, Zins M, Batty GD, Brunner EJ, Ferrie JE, Singh-Manoux A, Kivimäki M; IPD-Work Consortium. Job strain as a risk factor for type 2 diabetes: a pooled analysis of 124,808 men and women. *Diabetes Care*. 2014 Aug;37(8):2268-75.

ABBREVIATIONS

ACTH	Adrenocorticotropic hormone
Belstress	the Belgian Job Stress Study I
BMI	Body mass index
CI	Confidence interval
COPSOQ	Copenhagen Psychosocial Questionnaire Study
DCQ	Demand control questionnaire
DWECS	Danish Work Environment Cohort Study
FPS	Finnish Public Sector Study
Gazel	the Gaz et Electricité Cohort Study
HDL	High-density lipoproteins
HeSSup	Health and Social Support Study
HNR	Heinz Nixdorf Recall Study
HPA	Hypothalamus-pituitary-adrenocortical
HR	Hazard ratio
ICD	International Classification of Diseases
IPAW	Intervention Project on Absence and Well-being
IPD-Work	Individual-Participant-Data Meta-analysis in Working Populations
JCQ	Job content questionnaire
KORA	Cooperative Health Research in the Region Augsburg/MONICA
OGTT	Oral glucose tolerance test
OR	Odds ratio
POLS	Permanent Onderzoek LeefSituatie
PUMA	Burnout, Motivation, and Job Satisfaction Study
RR	Relative risk
SES	Socioeconomic status
SLOSH	Swedish Longitudinal Occupational Survey of Health
WH Ⅱ	Whitehall Ⅱ Study
WHO	World Health Organization
WOLF	Work, Lipids, and Fibrinogen Study (N=Norrland, S= Stockholm)

1 INTRODUCTION

Sufferers from diabetes have an abnormally high level of glucose in their blood. In cases of type 1 diabetes the pancreas does not produce insulin, whereas with type 2 diabetes the insulin production may be insufficient or the body is not responding properly to it. The pancreas produces extra insulin in the early stages of type 2 diabetes to compensate for the increased insulin resistance, but over time it fails to produce enough to keep the blood glucose at a normal level. In some cases the treatment involves lifestyle changes, but oral medication or insulin treatment is required as the disease progresses.[1,2]

Type 2 diabetes typically develops slowly. Its advanced stages are characterised by multiple complications, both microvascular (e.g. retinopathy, nephropathy, neuropathy) and macrovascular (e.g. atherosclerosis, coronary heart disease and stroke).[3,4] Complications can affect all vital organs including the brain, the eyes, the kidneys, the pancreas, the heart and the legs, and they may be life-changing.[5] Type 2 diabetes is associated with an increased risk of cardiovascular disease, dementia and mortality[6-10] and it ranks ninth as a cause of global mortality.[11]

Diabetes is a globally significant burden with regard to health and the quality of life. Its prevalence, especially of type 2, is growing worldwide. Currently approximately one in eleven adults has the disease, a figure that is expected to rise to one in ten by 2040.[1] In addition to about 415 million adults with diabetes, 318 million are expected to have impaired glucose tolerance, and thus to be at an increased risk of developing the disease.[1]

The major modifiable risk factors for type 2 diabetes include obesity and physical inactivity. Adopting healthy lifestyle habits, which is a key component in diabetes prevention, may take time.[12-18] However, several factors may affect both lifestyle and risk. It has been suggested, for example, that psychosocially stressful working conditions represent "causes of the causes", influencing indirectly through increased exposure to risk factors, and directly in the development of the disease. Yet, few studies have examined this hypothesis systematically in relation to type 2 diabetes. My aim in this thesis is to determine the extent to which job strain, the most widely studied work-related psychosocial predictor of ill health, is associated with diabetes and the risk factors, namely obesity and physical inactivity.

2 BACKGROUND

2.1 The job-strain model

The most common conceptualisation of work stress is the two-dimensional job-strain model, originally described by Karasek[19] in 1979 and further developed by Karasek and Theorell in 1990[20]. The two dimensions are psychological demands and job control. Psychological demands refer to whether the employee has to work very intensively or quickly, for example, or faces conflicting expectations. Job control, or decision latitude, describes the degree of decision-making authority and skill discretion in terms of the level of influence on what tasks to do and how, and the ability to use personal skills on the job. According to the model, work-related psychosocial stress arises from a combination of high psychological demands and low control over one's work (Figure 1).

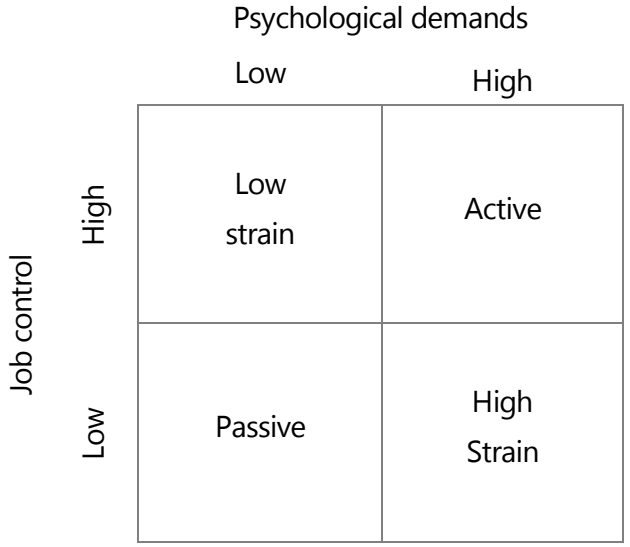

Figure 1. The Job Strain model (adapted from Karasek and Theorell 1990[20])

2.2 The measurement of job strain

At least two standardised and widely used questionnaires have been developed to measure the level of demands and control at work, and thus job strain: the 14-item Job Content Questionnaire (JCQ)[21] and the 11-item Demand Control Questionnaire (DCQ)[22]. Responses to these items are given on Likert-type response scales (see Table 1 for abbreviated questions and response options). A summary score is calculated over the response values for the demand items and for the control items, and both summary scores are dichotomised to define high and low job demands and job control. The combination of high demands and low control refers to job strain, whereas all other combinations define the reference category "no job strain". In a more refined classification, no-job-strain jobs are further divided into active (high demands, high control), passive (low demands, low control) and low strain (low demands, high control, reference), the so-called quadrant approach.

Study-specific variation in wording, translation, content, and response alternatives is typical in cohort studies from different countries, as is the use of different operational definitions. Some studies use only some of the questions from the original questionnaire. Other operationalizations in addition to the quadrant approach have also been applied in attempts to define job strain, including the quotient method (the job-demands score divided by the job-control score) and the subtraction approach (job demands minus job control). Median values are typically used to dichotomise the job-demands and job-control scores, but there is no consensus as to whether median values should be included or excluded to define the exposed category.

Table 1. Abbreviated items from the Job Content Questionnaire (JCQ) and Demand Control Questionnaire (DCQ)

JCQ	DCQ
Psychological demands	
Conflicting demands	Conflicting demands
Enough time	Enough time
No excessive amount of work	Too much effort
Working very fast	Work very fast
Working very hard	Work very intensively
Control	
A lot of say	Deciding what you do at work
High level of skill	High level of skill or expertise
Learn new things	Learn new things
Little decision freedom	Deciding how you do your work
Repetitive work	Same thing to do over and over again
Require you to be creative	Require you to take the initiative
Make your own decisions	-
Develop your own abilities	-
Variety	-
Response format:	
(1) strongly disagree	(1) never
(2) disagree	(2) seldom
(3) agree	(3) sometimes
(4) strongly agree	(4) often

2.3 Mechanisms linking job strain, health and diabetes

It is suggested that job strain influences health directly through stress-related biological mechanisms and indirectly via adverse changes in health-related behaviours.

Stressors, both psychological and physical, can cause acute stress reactions that are designed to protect the body by activating the fight-or-flight response. This automatic response prepares the body for fighting or fleeing, for example, in case of a sudden attack or threat. Stress response involves at least two physiological systems, the autonomic nervous system and the

hypothalamus-pituitary-adrenocortical (HPA) axis. The sympathetic nervous system, as part of the autonomic nervous system, is immediately activated: stress perception activates preganglionic sympathetic neurons in the spinal cord, which project to prevertebral or paravertebral ganglia and, in turn, to end organs including the heart, and to the adrenal medulla. This cascade of changes is accompanied by changes such as elevations in adrenaline and noradrenaline levels, an increase in the heart rate, peripheral vasoconstriction, vagal (parasympathetic) withdrawal, and increased energy mobilisation.[23-25]

On the HPA axis, stress perception also activates hypophysiotrophic neurons in the hypothalamus that secrete releasing hormones such as corticotropin. These hormones act on the anterior pituitary to promote the secretion of adrenocorticotropic hormone (ACTH). ACTH, in turn, acts on the adrenal cortex to initiate the synthesis and release of glucocorticoid hormones (in particular cortisol), which promote the mobilisation of stored energy.[23-25]

Stress reaction does not usually harm the body in the short term.[26] However, if a stress response is prolonged as a result of continuing or repeated stressors, then damage may ensue. The build-up of accumulated and chronic stressors and stress-responses is referred to as the allostatic load.[27,28] One of the consequences of HPA-axis dysregulation associated with chronic stress is elevated cortisol levels, which have been linked to various adverse health outcomes such as an increased risk of cardiovascular disease.[29,30]

Other potential outcomes of chronic stress include obesity and metabolic syndrome, both of which are highly relevant in relation to the risk of developing type 2 diabetes.[31-34] More specifically, increased cortisol secretion, as a result of HPA dysregulation, has been linked to higher central obesity as indicated by waist circumference or waist-to-hip ratio. An elevated waist-hip-ratio has been linked with high levels of stress and anxiety, but increased alcohol consumption and smoking also increase the risk of dysregulation of the HPA axis.[35] Nonetheless, these relationships are complex. According to a recent systematic review of the association between the HPA axis dysregulation and cortisol activity in obesity the current evidence remains inconclusive, although the relationship between obesity and adipocyte cortisol appears consistent. The authors of that review also found a general pattern of a positive association between higher levels of abdominal fat and greater responsivity of the HPA axis.[33]

Type 2 diabetes is typically preceded by 'prediabetes', a condition in which glycaemic variables are higher than normal, but do not exceed the limits for

diabetes diagnosis.[2] Although prediabetes increases the risk of progressing to manifest diabetes, it does not always happen and favourable lifestyle changes can normalise the situation back to normoglycaemia, for example. Many risk factors for developing diabetes and metabolic syndrome are the same as those for developing cardiovascular disease, and include age, sex, obesity, physical inactivity, smoking, elevated blood pressure and dyslipidemia.[36] Clinical guidelines for diabetes prevention emphasise obesity and physical inactivity as key primary targets.[37] However, the extent to which job strain and other psychosocial stressors hinder successful weight management and the adoption of a physically active lifestyle remains poorly understood.[38-45] If job strain increases the risk of obesity and physical inactivity, it could also indirectly increase the risk of type 2 diabetes among people who experience it.

2.4 Evidence on the association between job strain and obesity

The most commonly utilised measure of adiposity is the body mass index (BMI), calculated from weight and height (weight in kg/height in meters squared). A BMI value of 30kg/m^2 or higher is generally used to define obesity, which is an increasingly serious public-health challenge globally.[46,47] Obesity is linked to a reduced quality of life and to disability, and is a major risk factor for several chronic illnesses such as diabetes, cardiovascular disease and cancer[47-52]. It has been hypothesised that there is a link between job strain and obesity arising from the tendency of stress to contribute to unhealthy lifestyles,[53,54] such as physical inactivity[55] and unhealthy eating habits[56], which in turn increase the risk of weight gain. However, stress may also reduce the appetite and cause some people to eat less, thus leading to weight loss.[57-59] Furthermore, it has been suggested that the association between stress and weight change could be bi-directional because obesity may reduce work capacity[60] thus strengthening the feeling of stress. The direction of the effect could be dependent on sex, baseline BMI or other factors. These opposite effects may override each other and lead to the conclusion of no association. Yet another explanation relates to socioeconomic disadvantage, which could be a common contributory factor to both stress and obesity potentially leading to a spurious link between the two.

Evidence on the association between work stress and obesity has been inconsistent thus far, based largely on small samples or concentrated on forms of work stress other than job strain. These include the separate components of job strain (job demands and job control), iso-strain, social support, long working hours, and job insecurity, for example. Some positive findings have

been reported to suggest that job strain is related to a higher BMI[61], but results suggesting no association between the two have also been reported[62-64]. It was reported in one study that high strain was associated with higher obesity risk and a higher mean BMI in the crude models, but the inclusion of potential intermediate variables (physical activity, sedentary behaviour and diet quality) diminished the effect.[65] Different associations among men and women have also been reported[66]. Furthermore, different results have been observed depending on the definition of job strain[67]. Some longitudinal studies have examined the association between changes in job strain and BMI or obesity status, but the settings and definitions have varied. [58,68,69]

The Whitehall II study[58] examined the posited bidirectional association between work stress and weight change. The analyses were based on longitudinal data from 7,965 participants aged 35-55 at baseline. Job strain was assessed at both baseline and follow-up five years later. According to the results, the effect of job strain on weight gain and weight loss may depend on baseline BMI. Among men in the leanest quintile (BMI<22kg/m^2) at baseline, high job strain was associated with weight loss by the follow-up, whereas it was associated with subsequent weight gain among those in the highest BMI quintile (>27kg/m^2). Similar bidirectional associations were not observed in women.

Shields[68] used Canadian National Population Health Survey data to examine the associations between work conditions and changes in health-behaviour factors, including job strain and weight change. The study population comprised 3,830 adults aged 25-54 years who worked 35 or more hours per week. The follow-up period was two years. To classify unhealthy weight change, the average percentage gain between baseline and follow-up was calculated for men and women. Individuals with a percentage weight gain of more than one standard deviation above the mean were classified as having unhealthy weight gain. People with a BMI <20kg/m^2 at baseline were excluded from this analysis. Baseline job strain did not appear to be associated with unhealthy weight gain among the men (OR=1.0, 95% CI 0.6-1.7), but the association was borderline significant among the women (OR=1.8, 95% CI 1.0-3.2).

Ishizaki[69] et al. examined the association of change in job strain with weight gain. The data related to 2,200 men and 1,371 women aged 30-53 working in a factory. The time interval between the two measures was six years. The job-strain score was calculated as a value of job demands divided by job control and dichotomised at the median values for men and women separately. It was

further categorised into three groups as follows: Group I: low score in both the first and second examinations, Group II: low score in the first examination and high score in the second or vice versa, and Group III: high score in both the first and second examinations. There was no statistically significant association between job strain and change in body mass index. However, there was a bigger increase in waist circumference among those of both genders with high job strain in both measurements (Group III) compared to those consistently reporting low job strain (Group I).

Eek[64] et al. used data from a cohort of 9,913 Swedish adults comprising baseline and follow-up surveys at a five-year interval. At baseline, BMI was not associated with job strain. The job-strain pattern over time had no significant association with BMI increase either, except among middle-aged women ($p=0.034$): women with longstanding strain ($p=0.019$) and those who experienced strain only at baseline ($p=0.04$) showed a greater increase in BMI than those with no job strain at baseline or follow-up.

In sum, current evidence on the association between job strain, weight change and obesity is inconclusive.

2.5 Evidence on the association between job strain and physical inactivity

Physical inactivity is a risk factor for several chronic illnesses including cardiovascular diseases, type 2 diabetes and some cancers, and even premature death[70-77]. The amount of physical activity is ascertained in a variety of ways in questionnaire-based surveys, usually on questions about the frequency and intensity of weekly or daily activity.

A link between job strain and physical inactivity is plausible because stressed individuals may suffer from fatigue and need more time for recovery. This, in turn, could increase the likelihood of leisure-time passivity and sedentary behaviour. It has also been hypothesised that passive, unchallenging jobs with few demands and little control over one's work could lead to reduced self-efficacy, resulting in a passive lifestyle.[20,78] However, these hypotheses have not been fully confirmed based on empirical evidence. Some studies have produced evidence of an association between job strain and physical inactivity[53,63,79-84], although some of these associations were attenuated after adjustment[79,81,83]. In addition, diverse results have been reported when the association was studied in sub-groups[63,79,82-84]. According to the Whitehall II Study of British civil servants, for example, participants working in passive jobs

were particularly likely to be physically inactive during their leisure time.[85] Several null findings on the association between job strain and leisure-time physical activity have also been reported.[78,86,87]

2.6 Evidence on the association between job strain and diabetes

Given the uncertain associations between job strain and the main risk factors of diabetes (obesity and physical inactivity), it seems unlikely that a strong association with type 2 diabetes would emerge via these factors. This does not exclude the possibility that job strain directly affects the risk of diabetes. Indeed, it is biologically plausible to assume an association between work stress and an increased risk of developing type 2 diabetes[88] in that response to stress increases the secretion of the fight-or-flight hormone cortisol, which in turn stimulates glucose production in the liver and antagonises the action of insulin in peripheral tissues.[27,89,90] These effects could also be exacerbated indirectly via lifestyle changes. However, evidence supporting an association between job strain and the risk of type 2 diabetes is based on inconsistent results and small samples: some studies show an association[91-94] whereas others do not.[95-98] However, it is worth noting that all the positive associations were only identified in women, and within the same studies the results among men were null.

Leynen et al. analysed cross-sectional data from a large Belgian cohort. Information on diabetes was based on self-reports, its prevalence among men being 2.6 per cent (n=16,335) compared with 2.1 per cent among women (n=5084). Among women a significant, twofold prevalence was observed in the high-strain group compared to the non-high group, whereas there was no difference among the men between workers in the high-strain category and all other categories combined.[91]

Agardh et al. reported further cross-sectional analyses involving a Swedish all-female cohort (n=4821). Diabetes was ascertained by means of a 75-g oral glucose tolerance test, and participants with known diabetes at baseline were excluded from the analyses. According to the results, job strain was not associated with undiagnosed type 2 diabetes.[95]

Kawakami et al. conducted the first prospective cohort study on the association between job strain and diabetes in 1999. The cohort comprised 2597 men who were followed up for eight years. They were workers at an electrical company in Japan, and all were given an annual medical check-up

that included screening for diabetes. No statistically significant association between job strain and the incidence of type 2 diabetes was observed (HR 1.34, 95% CI 0.50-3.55), although a moderate association could not be ruled out.[96]

Kroenke et al. reported prospective results based on 62,574 women participating in the Nurses' Health Study. Diagnosis of diabetes was self-reported in biennial questionnaires. The analyses included comparisons between the high-strain and the low-strain categories, and no elevated risk was found (RR=1.11, 95% CI 0.80-1.52), although again a small effect could not be excluded.[97]

The Whitehall Ⅱ study is one of the cohort studies included in the Individual-Participant-Data Meta-analysis in Working Populations (IPD-Work) Consortium, a collaborative research venture used as a source in this dissertation. Previously, Heraclides et al. had examined the association between job strain and diabetes in a study in which the diagnosis of diabetes was based on repeated oral glucose-tolerance tests supplemented with self-reports. The sample consisted of 5,895 middle-aged participants. According to the results, job strain was associated with an elevated diabetes risk among the women (HR=1.59, 95% CI 1.03-2.45) but not among the men (HR=0.82, 95% CI 0.59-1.15), or among women and men combined (HR=1.04, 95% CI 0.80-1.34).[92] This association was later further analysed to examine the interaction between work stress and obesity in relation to the risk of type 2 diabetes. The association between job strain and 18-year incident type 2 diabetes was analysed and stratified by obesity status (BMI <30 kg/m^2 vs. BMI ≥ 30 kg/m^2) and sex. Overall work stress was associated with diabetes risk among the women (HR=1.41, 95% CI 1.02-1.95), but not among the men (HR=0.87, 95% CI 0.69-1.11). However, there was interaction between job strain and BMI in the stratified analyses: job strain was associated with a lower risk of diabetes in the non-obese (HR=0.70, 95% CI 0.53-0.93) but not in the obese male participants ($P_{interaction}=0.17$), whereas it was associated with a higher risk of diabetes in the obese (HR=2.01, 95% CI 1.06-3.92) but not in the non-obese females ($P_{interaction}=0.005$).[99]

Nordberg et al. (2007) reported on a more recent longitudinal study based on a sample of Swedish residents from the county of Västerbotten, where all inhabitants aged 40, 50 and 60 were invited to participate in a health survey. A Swedish version of the Karasek demand/control model was applied in a questionnaire, in which job strain was presented as "tense" working conditions (a combination of high demands and low decision latitude). The participants

were followed up for a mean of 7.8 years. Job strain was not associated with incident type 2 diabetes among the men (OR=1.1, 95% CI 0.4-2.9) although a borderline significant but imprecise association was found among the women (OR=3.6, 95% CI 1.0-13.3).[93]

Eriksson et al. presented results from a population-based longitudinal study in 2013. Baseline glucose tolerance in 5,432 participants was measured by means of the OGTT at baseline, and a follow-up examination was conducted 8-10 years later, Dichotomous job strain was associated with an elevated risk of type 2 diabetes among the women (OR=4.2, 95% CI 2.0-8.7), but no elevation in risk was noticed among the men (OR=0.8, 95% CI 0.4-1.7). However, it is worth noting that when high strain was compared to low strain (instead of all the other categories combined), the association among women was markedly weaker (OR=2.1, 95% CI 0.9-4.8).[94]

Smith et al. analysed longitudinal data from Ontario, Canada in which a total of 7,443 participants were linked to the local Health Insurance Plan database for physician services and the hospital admission register. During the mean follow-up of nine years, job strain was not associated with an elevated risk of type 2 diabetes among men or women, although no effect estimates were provided.[98]

In 2012 Cosgrove et al. conducted a meta-analysis of cross-sectional and prospective studies on the association between work-related stress and diabetes. Of the five articles on job strain and diabetes included in the analysis three were based on longitudinal[92,96,97] and two on cross-sectional[91,95] data. Nordberg et al. had published their paper in 2007, and some of the results were included in the meta-analysis. However, findings related to job strain were omitted because the Swedish version of the Karasek demand/control model was not considered comparable to job strain. The results reported in the Agardh paper were not included in the summary either because only minimally adjusted estimates were given in the study. The authors of the meta-analysis concluded that there was no association between job strain and type 2 diabetes, with an overall estimate of RR=1.08 (95% CI: 0.84-1.32).[100]

We updated the meta-analysis, including one new study and the two omitted studies and stratified the analysis by sex. According to that evidence, the association may depend on sex. As shown in Figure 2, the overall estimate from a random-effects meta-analysis yielded RR=1.38 (95% CI 1.04-1.82): RR=0.92 (95% CI: 0.76-1.12) among men and RR=1.91 (95% CI 1.29-2.83) among women. High heterogeneity between the study-specific estimates was

observed among the results on women (I^2=65%, p=0.015), but not among men (I^2=0%, p=0.84). This result does not include the non-significant estimates reported by Smith et al[98], because no estimate was given: their inclusion would have slightly diminished the summary estimate.

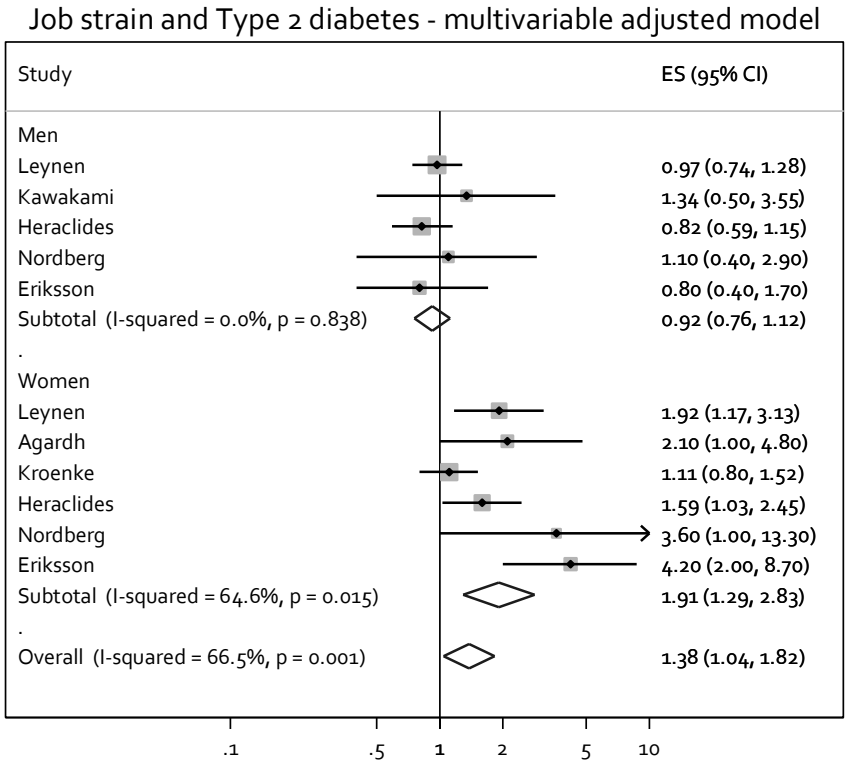

Figure 2. Meta-analysis of the relative risk of type 2 diabetes in people with job strain compared to those with no job strain, as reported in published studies

2.7 A summary of the evidence on job strain, BMI, physical inactivity and incident diabetes

There is a strong need for a better understanding of the associations between job strain and adverse lifestyle factors given that the evidence is inconsistent and is thus far based on small samples and imprecise estimates. According to the literature review, cross-sectional and longitudinal evidence on job strain and BMI is mixed, including both positive and null findings, and variation in the associations between subgroups such as between men and women. The difference between the study cohorts and the definitions in the job-strain measure may explain some of the inconsistency. Individuals may also respond to stress differently – some may eat more, others lose their appetite and still others might increase their consumption of comfort food or alcohol to relieve the feeling of stress.

Large datasets are needed to reliably demonstrate the presence or lack of an association between job strain and BMI, with reliable estimates of the magnitude of the effect. A major challenge complicating comparison of the results is the inconsistency in the definition of job strain and the lack of prospective analyses. More longitudinal analyses with multiple datawaves are needed to facilitate examination of the potential bidirectional association between job strain and obesity.

Empirical evidence on the association between job strain and physical inactivity is also limited and suffers from similar challenges as in the case of its association with obesity. Some evidence of a link with physical inactivity has been produced, however, although some studies failed to detect such an association.

Finally, an association between job strain and diabetes would be plausible but the evidence remains uncertain. There are also indications that the association might be more apparent in women than in men.

3 THE BENEFITS OF A MULTICOHORT STUDY DESIGN

There are several ways of addressing the limitations in the evidence on job strain, obesity, physical inactivity and diabetes. First, predefined, harmonised measures of covariates, exposures and outcome variables should be used when possible, thus excluding bias arising from *post hoc* exposure definition, which is better avoided when the assessment of job strain is consistently defined across studies.

Second, the pooling of multiple cohorts to investigate the relationship between work-related psychosocial factors and health outcomes offers multiple benefits. Calculating the summary estimates over the risk estimates based on data from individual cohorts reduces the risk of random error. Data from multiple independent cohort studies collectively comprise a very large analytical sample, thus providing a high level of statistical precision via narrower confidence intervals, and enabling statistical power for subgroup analysis to further examine the robustness of the associations. A large sample size also generates sufficient statistical power to detect small effects and convincingly demonstrate a lack of effect. Large samples are particularly suited to exposures such as job strain, when the exposed population is relatively small (prevalence approximately 16-17%): very large datasets are needed to facilitate subgroup analyses. An advantage of using a two-stage meta-analysis (i.e. analysing the associations within each study and then pooling the study-specific estimates) is that the associations can be illustrated by means of forest-plots that visualise the patterns.

4 THE AIMS OF THE STUDY

The dataset used in this thesis originates from the IPD-Work Consortium, which was set up to investigate associations between work-related psychosocial factors and disease outcomes.

A pre-defined, two-stage data-acquisition protocol was used to reduce bias related to post hoc decision-making. The baseline data on job strain, socio-demographic characteristics and lifestyle factors were acquired and harmonised during the first stage, whereas information on disease outcomes was acquired and analysed during the second stage. This two-step procedure mimics the randomised controlled trial in which the protocols defining the intervention and the outcomes are fixed and registered prior to the start of the study.

With a view to overcoming some of the limitations detected in previous evidence on job strain, diabetes risk factors and incident diabetes, multi-cohort data from the IPD-Work Consortium was analysed to determine whether individuals with job strain have increased odds of being obese and physically inactive, and higher levels of other risk factors for diabetes. A further aim was to determine whether individuals with job strain have an increased risk of type 2 diabetes.

The following five objectives were set.

Objective 1: To harmonise a cross-cohort measurement instrument for job strain (Sub-study I).

Objectives 2 and 3: To determine the cross-sectional and longitudinal associations between job strain and key lifestyle-related risk factors for diabetes such as BMI (Sub-study II) and physical inactivity (Sub-study III).

Objective 4: To compare the strength of the associations between job strain and both obesity and physical inactivity to associations with traditional cardiovascular risk factors such as diabetes status, blood pressure and blood lipid concentrations (Sub-study IV).

Objective 5: To determine the association between job strain and incident diabetes and the extent to which it is attributable to BMI, physical inactivity and other lifestyle factors (Sub-study V).

Sub-studies I-IV are thus based on the first-step analyses of the IPD-Work Consortium conducted prior to the linkage of the data with the diabetes

outcome. Sub-study V is based on the second-step analyses conducted after the linkage to the disease data.

5 METHODS

The IPD-Work Consortium was established at the annual Four Centers Meeting workshop held in London in November 2008. The overall aim is to aggregate data from several studies and thereby obtain reliable estimates of the influence of work-related psychosocial risk factors on chronic diseases, mental health, disability and mortality. The consortium initially comprised 17 European cohort studies, but new studies have subsequently been added.

5.1 Study population

There is some variation in the constitution of the studies included in the analyses, depending on the available data. The studies are listed in Table 2.

Table 2. Study population

Study and country	Baseline	N*	Age range (years)	Sub-study reference**
Belstress, Belgium[101]	1994-1998	21 419	35-59	I, II, III, IV
COPSOQ-I, Denmark[102]	1997	1858	20-60	V
COPSOQ-II, Denmark[103]	2004-2005	3818	20-60	V
DWECS, Denmark[104]	2000	5606	18-59	II, III, V
FPS, Finland[105]	2000	48 592	17-65	II, III, V
Gazel, France[106]	1997	20 625	35-50	I, II, III, V
HeSSup, Finland[107]	1998	17 102	20-54	I, II, III, V
HNR, Germany[108]	2000-2003	4814	45-75	II, III, IV
IPAW, Denmark[109]	1996-1997	2721	18-68	II, III, V
KORA 1-3, Germany[110]	1984…1995	13 818	25-74	IV
POLS, the Netherlands[111]	1997-2002	59 441	15-85	II, III
PUMA, Denmark[112]	1999-2000	1914	18-69	II, III, V
SLOSH, Sweden[113]	2006 and 2008	12 736	16-64	I, II, III, V
Still Working, Finland[114]	1986	9 282	18-65	III, V
Whitehall II, the UK[115]	1985-1988	10 308	34-55	II, III, IV, V
WOLF N, Sweden[116]	1996-1998	4718	19-65	I, II, III, IV, V
WOLF S, Sweden[117]	1992-1995	5698	19-70	I, II, III, IV, V

*There is variation in the numbers of participants included in the different studies

** (I) Fransson et al, BMC Public Health, 2012[118]; (II) Nyberg et al, JIM, 2012[119]; (III) Fransson et al, AJE, 2012[120]; (IV) Nyberg et al, PLOS ONE, 2013[121]; (V) Nyberg et al, Diabetes Care, 2014[122]

5.2 The measurement of job strain

The job-strain variable was validated before any analyses related to the IPD-Work Consortium were conducted.[118] The complete scales for the validated measures of job demands and job control were based on five items from the psychological-demands scales, and six items from the control scales of the Job Characteristics Questionnaire (JCQ) and the Demand-Control Questionnaire (DCQ). The JCQ has three additional control items that do not have a corresponding item in the DCQ and were thus omitted to improve the harmonisation of the control scales across the studies. Table 3 lists the items included in the complete harmonised job-strain variable.

Table 3. Abbreviated items from the Job Content Questionnaire (JCQ) and the Demand Control Questionnaire (DCQ) included in the IPD-Work Consortium

JCQ	DCQ
Psychological demands	
Conflicting demands	Conflicting demands
Enough time	Enough time
No excessive amount of work	Too much effort
Working very fast	Work very fast
Working very hard	Work very intensively
Control	
A lot of say	Deciding what you do at work
High level of skill	High level of skill or expertise
Learn new things	Learn new things
Little decision freedom	Deciding how you do your work
Repetitive work	Same thing to do over and over again
Require you to be creative	Require you to take the initiative

Proxy items were used when the original questionnaire was not applied but similar questions were asked. The proxy items were judged by the five coordinating authors to resemble the original questions in wording to such an extent that they could be used. For example, the question on conflicting demands was worded thus in the Still Working study: "Do your superiors or workmates give you contradictory orders or instructions?" and the corresponding item in the DCQ is "Does your work often involve conflicting demands?".

The partial scales were constructed based on the availability of JCQ/DCQ or corresponding proxy scales in each IPD-Work study that did not include the complete or original scales. This resulted in six partial demand scales, five partial control scales and ten partial job-strain scales.

The six cohort studies with complete job-demand and job-control scales that were available were the Belstress (Belgium)[101], the Gazel (France)[106], the HeSSup (Finland)[107], the SLOSH (Sweden)[113] and the WOLF N and WOLF S (Sweden)[116,117]; and eleven available cohort studies with partial scales were COPSOQ-I (Denmark)[102], DWECS (Denmark)[104], Still working (Finland)[114], FPS (Finland)[105], HNR (Germany)[108], IPAW (Denmark)[109], KORA (Germany)[110], NWCS (the Netherlands)[123], POLS (the Netherlands)[111], PUMA (Denmark)[112] and the Whitehall Ⅱ (the UK)[115].

The mean response scores for the job-demand items and the job-control items were calculated for each study participant. For both scales, a mean response score was calculated for participants who had answered at least half of the demand or control questions on that specific scale. However, when only two items were used in a partial scale, both had to be answered for the mean score to be calculated. A missing score on either scale resulted in a missing value in the job-strain variable.

The presence of job strain was defined as having high demands (i.e., higher than the study-specific median of the demands scores) and low control (i.e., lower than the study-specific median of the control scores). This dichotomous definition of job strain based on the quadrant approach has been widely used and is predominantly applied in the IPD-Work Consortium. Job strain was used as a categorical variable in the analyses conducted for Sub-study Ⅲ: high strain, active, passive and low strain (the reference).

5.3 The assessment of BMI

Height and weight were either self-reported or measured by a clinician or a nurse in a health examination, depending on the cohort study. Self-reported data were used in COPSOQ-Ⅱ, DWECS, FPS, Gazel, HeSSup, IPAW, POLS, PUMA and SLOSH, and data from measured height and weight were available from Belstress, HNR, KORA 1-3, Whitehall Ⅱ, WOLF-N and WOLF-S. Weight and height were coded in categories in POLS, the category mean being used for calculating BMI in that cohort. Data for calculating BMI was not available for the COPSOQ-I and Still Working studies. Body mass index was calculated in accordance with the common formula: weight in kilograms divided by

height in meters squared, and participants with extreme values <15 or >50 kg/m^2 were excluded from the classification. BMI was classified according to World Health Organization (WHO) recommendations:[47] participants with a BMI <18.5 kg/m^2 were categorised as underweight, those with a BMI between 18.5 and <25 kg/m^2 were classified as of normal weight and those with a BMI between 25 and <30 kg/m^2 as overweight. In addition, in line with the WHO international classification of adult obesity[47] we included three categories of obesity: class I (BMI 30 to <35 kg/m^2), class II (BMI 35 to <40 kg/m^2) and class III (BMI at least 40 kg/m^2). We used a dichotomous variable for obesity in some analyses, in which the categories were combined and compared to non-obese categories. Normal weight was defined as the reference category.

5.4 The measurement of physical inactivity

Assessments of physical activity were based on self-reports, and there was variation in these questions between the studies. Some of the studies included questions on specific types of physical activity (e.g. walking and cycling) whereas others only included questions about overall levels of sports activities and exercise. Respondents reporting no or very little moderate or vigorous leisure-time physical activity or exercise were defined as physically inactive. Table 4 lists the definitions used in each study.

Table 4. Operational definitions of leisure-time physical inactivity in the IPD-Work Consortium cohort studies

Study	Baseline	Leisure-time physical inactivity
WOLF S[117]	1992-1995	No or very little exercise, only occasional walks
WOLF N[116]	1996-1998	No or very little exercise, only occasional walks
Whitehall II[115]	1985-1988	No moderate or vigorous exercise
Still Working[114]	1986	Sport activities less than a couple of times per month
SLOSH[113]	2006, 2008	No or very little exercise, only occasional walks
PUMA[112]	1999-2000	Almost completely physically passive or light physical activity for less than 2 hours/week (e.g., reading, television, cinema)
POLS[111]	1997-2002	No exercise and less than 1 hour walking and less than 1 hour cycling for fun per week
IPAW[109]	1996-1997	Almost completely physically passive or light physical activity for less than 2 hours/week (e.g., reading, television, cinema)
HNR[108]	2000-2003	Less than 0.5 hours of moderate or vigorous physical activity per week
HeSSup[107]	1998	Less than 0.5 hours of each (brisk walking, jogging, or running) per week
Gazel[106]	1996	No sport activities
FPS[105]	2000	Less than 0.5 hours of each (brisk walking, jogging, or running) per week
DWECS[104]	2000	Almost completely physically passive or light physical activity for less than 2 hours/week (e.g., reading, television, cinema)
Belstress[101]	1994-1998	No weekly physical activity

5.5 The measurement of other cardiovascular risk factors and covariates

5.5.1 Assessment of demographic characteristics

Information on age and sex was self-reported (Belstress, HeSSup, POLS, and Whitehall Ⅱ), obtained from registers or recorded in a medical examination (COPSOQ-I, COPSOQ-Ⅱ, DWECS, FPS, Gazel, HNR, IPAW, KORA 1-3, PUMA, SLOSH, Still Working, WOLF N, and WOLF S). Information on socioeconomic status (SES), based on occupational position, was obtained from employers' records or other registers, or was self-reported. In the HeSSup study it was based on the highest educational level reported by the participant. SES was categorised as low, intermediate or high. Self-employed participants and those with missing data were included in the "other" SES category. Participants with missing values for either age or sex (less than 1% of all respondents) were excluded from all the analyses.

Shift workers were identified based on self-reports, although there was a large amount of variation between the studies in the categories used in this question.

5.5.2 Assessment of other lifestyle variables

Complementing the data on BMI and physical inactivity, information on smoking and alcohol use was collected and harmonised across the studies. Regardless of the nature of the lifestyle factors and the differences in the questions asked, harmonised variables of these data were obtained.[119,120,124,125]

Smoking status was classified in three categories: former, current and never smokers. Former and never smokers were pooled as non-smokers in a dichotomous version of this variable.[124]

Information on alcohol use was elicited in questions concerning the total number of alcoholic drinks the participant consumed in a week. Account was taken of the type of drink, one drink being defined as approximately equivalent to one unit or one glass of an alcoholic drink or 10 g of ethanol. Alcohol use was categorised as none, moderate (women: 1-14, men: 1-21 drinks/week), intermediate (women: 15-20, men: 22-27 drinks/week) and heavy (women: >20, men: >27 drinks/week).[125]

5.5.3 Assessment of biological cardiovascular-disease risk factors

Participants in the Belstress, HNR, KORA 1-3, WOLF N, WOLF S and Whitehall II studies underwent a clinical examination at baseline. Their height, weight and blood pressure were measured, and a blood sample was taken. Hypertension was defined as having systolic (diastolic) blood pressure of at least 140 (90) mmHg, or being on antihypertensive medication. Total and HDL-cholesterol levels were measured in all the studies, but triglyceride values only in four (HNR, WOLF N, WOLF S and Whitehall II). Cholesterol ratio was defined as the total divided by HDL cholesterol. Diabetes and the use of antihypertensive or lipid-lowering medication were based on self-reports in Sub-study IV. Baseline diabetes status was additionally assessed in the Whitehall II study by means of a 75g two-hour oral glucose tolerance test (OGTT). Pulse pressure (systolic minus diastolic blood pressure) was assessed in addition to the traditional risk factors because high pulse pressure is an independent marker of atherosclerosis.[126]

To examine overall cardiovascular disease risk, we constructed the Framingham cardiovascular disease risk score on the basis of age, total cholesterol, HDL cholesterol, systolic blood pressure, use of hypertensive medication, smoking and diabetes status. In accordance with the clinical guidelines, we defined "high" overall risk as a Framingham score of at least 20%.[127]

5.6 Ascertainment of incident diabetes

Diabetes was defined as the first record of type 2 diabetes, diagnosed corresponding to ICD-10 code E11. Records were collected from hospital admissions and discharge registers, and from mortality registers with a mention of a diagnosis of diabetes in any of the diagnosis codes. Participants in the three Finnish datasets (FPS, HeSSup, and Still Working) were additionally defined as cases of incident type 2 diabetes the first time they appeared in the drug reimbursement register as eligible for type 2 diabetes medication.[128] In the Whitehall II study, type 2 diabetes was ascertained by a 75g two-hour oral glucose-tolerance test administered every five years[88] using the WHO criteria. This information was complemented with self-reports of a diabetes diagnosis and medication. ICD codes were only available from the mortality register in the Gazel study, and nonfatal cases were based on self-reports from annual questionnaires.

The date of diagnosis was defined as the date of the first record in any of the previously mentioned sources, and follow-up time was calculated from baseline assessment until the first record of type 2 diabetes, death, or end of follow-up, whichever came first.

Both Type 1 and Type 2 diabetes cases at baseline were excluded from the analyses to facilitate identification of incident type 2 diabetes cases. Prevalent (existing) cases were defined using hospital, mortality and drug-reimbursement registers, supplemented with self-reports from questionnaires or baseline medical assignment.

5.7 Statistical analysis

In Sub-study I, the relationship between the complete and partial scales for the demands and control scales was ascertained from Pearson correlation coefficients with accompanying 95-per-cent confidence intervals, calculated using Fisher's transformation. Sensitivity, specificity and Kappa (κ) statistics were calculated to evaluate the agreement between the job-strain definitions based on the complete versus the partial scales. The Kappa values were utilized as follows: slight agreement (0.00-0.20), fair (0.21-0.40), moderate (0.41-0.60), good/substantial strength of agreement (0.61-0.80), and very good/almost perfect agreement (0.81-1.00).[129]

Both one- and two-stage meta-analyses of individual participant data were conducted.[130-132] One-stage meta-analysis involves pooling all available individual-level data into one dataset, an approach that was used in the studies addressing objectives 1, 2, 3 and 5. In the two-stage analyses, effect estimates and their standard errors were estimated separately for each study using a specific method (the first stage), and these study-specific results were then pooled by means of random-effects meta-analysis (the second stage)[133]. This approach was used in the sub-studies addressing objectives 2, 3 and 5. Heterogeneity among the study-specific estimates in the two-stage approach was assessed using the I^2 statistic.[134]

Both one- and two-stage meta-analyses of individual participant data were conducted in Sub-studies II and III, and logistic regression was the main method used. The cross-sectional analysis was a two-stage meta-analysis that included all cohort studies irrespective of whether individual-level or aggregate data were available. For each study, the effect estimates and their standard errors were obtained using logistic regression (the first stage) and

these study-specific results were then pooled using random-effects meta-analysis (the second stage)[133].

In Sub-studies II and III, additional repeated measures of job strain, BMI and physical inactivity were available for some of the cohort studies (repeated measure of BMI for Belstress, FPS, HeSSup and Whitehall II, and repeated measure of physical inactivity for Belstress, FPS, HeSSup, SLOSH, Whitehall II and WOLF N). The same definitions of job strain, BMI and physical inactivity were used both at baseline and at follow-up, and the same study-specific cut-off points that were used to define job strain at baseline were used at follow-up.

In Sub-study II, summary odds ratios with 95-per-cent confidence intervals were calculated for job strain in each BMI category. The odds ratios were adjusted for sex, age, SES and smoking. To examine heterogeneity caused by the measurement method, the analyses were additionally run separately for the studies with measured height and weight and for those with self-reported values. Subgroup differences were tested in the pooled dataset using a mixed-effects logistic regression model, with the study as the random effect and including an interaction term (BMI*covariate). A similar approach without the interaction term was used for the longitudinal analyses.

In Sub-study III the summary odds ratios and 95-per-cent confidence intervals were calculated for participants who were categorised as having passive, active or high-strain jobs, comparing them with individuals with low-strain jobs. The odds ratios were adjusted for sex and age, and for sex, age, SES and smoking. The cross-sectional associations were further stratified by sex, age (<50 vs. ≥50 years), level of SES and smoking status (never smokers, ex-smokers and current smokers).

The analyses in Sub-study IV were conducted using mixed-effects linear and logistic regression models in a pooled dataset, the study being treated as a random effect variable. The models were adjusted for age and sex, and also for SES. The robustness of each association was further examined by means of multivariable adjustment.

Triglyceride concentrations were logarithmically transformed due to the skewed distribution. In the main analysis, participants reporting the use of antihypertensive medication were excluded when the outcome was blood pressure or pulse pressure, and those reporting the use of lipid-lowering medication were excluded when the outcome was any measure of lipids. However, the sensitivity analyses included these participants.

In Sub-study V the association between job strain and incident type 2 diabetes was analysed using Cox proportional hazards regression models within each study. The study-specific effect estimates and their standard errors were pooled in fixed- and random-effect meta-analyses. Given the low heterogeneity, the respective estimates were virtually identical and the results from the fixed-effect models were reported.

The main analyses in Sub-study V were adjusted for sex, age and SES, and further for lifestyle variables (BMI category, physical inactivity, smoking and alcohol consumption) and biological risk factors. Stratified analyses by sex and age group (<50 years vs. ≥50 years) were conducted. Reverse causation was accounted for by excluding the events during the first three years of follow-up.

The risk of diabetes was also examined in the four groups created by combining data on job strain and each dichotomised lifestyle factor. The lifestyle risk factors used in these analyses were current smoking (yes vs. no), heavy alcohol use (≥21 drinks per week for women and ≥28 drinks per week for men vs. other), obesity (BMI ≥30 vs. <30kg/m^2) and physical inactivity (yes vs. no).

SAS versions 9.1 and 9.2 (SAS Institute Inc., Cary, NC, USA), the Stata versions 11 and 13, R version 2.11 (library Meta, http://www.r-project.org) and SPSS 17 were used for the analyses.

6 RESULTS

6.1 Demographic characteristics

The number of participants included in the analyses varied between the five sub-studies. The characteristics of the participants are listed in Table 5.

Table 5. The characteristics of the participants in Sub-studies I-V

Sub-study	Number of cohort studies	Number of participants	Women (%)	Mean age (years)
I	17	70 751	NA	NA
II	13	161 746	51	43.7
III	14	170 162	50	43.5
IV	8	47 045	29	45.1
V	13	124 808	57	44.1

6.2 Validation of the job-strain measure

The job-strain measure was validated for the IPD-Work studies in Sub-study I. The analyses were based on six cohort studies (N=70 751) with information on the complete scales and 11 cohort studies that were used to constrain the partial scales. Items included in the complete scales are shown in Table 3 and those included in the proxy scales in Table 6. There was high correlation between the partial and the complete job-demands and job-control scales. The agreement for the dichotomous job-strain variable was very good or at least adequate.

Table 6. Job-demand and control items used in the formulation of the harmonised job-strain variable in the IPD-Work Consortium (adapted from Sub-study I)

Study	Questionnaire*	Demand items**	Control items†
Compete scale			
Belstress[101]	JCQ	1,2,3,4,5	1,2,3,4,5,6
Gazel[106]	JCQ	1,2,3,4,5	1,2,3,4,5,6
HeSSup[107]	JCQ	1,2,3,4,5	1,2,3,4,5,6
SLOSH[113]	DCQ	1,2,3,4,5	1,2,3,4,5,6
WOLF N[116]	DCQ	1,2,3,4,5	1,2,3,4,5,6
WOLF S[117]	DCQ	1,2,3,4,5	1,2,3,4,5,6
Partial scale			
FPS[105]	JCQ	2,3,4	1,2,3,4,5,6
HNR[108]	JCQ	1,2,3,4	1,2,3,4,5,6
IPAW[109]	DCQ	1,4	1,2,3,4,5,6
KORA[110]	Mainly JCQ	1,2,3,4,5	1,2,3,4,6
COPSOQ[102]	Mainly DCQ	1,4,5	1,2,3,4,5,6
DWECS [104]	Mainly DCQ	1,4,5	1,2,3,4,5
PUMA[112]	Mainly DCQ	1,4,5	1,2,3,4,5
WH II[115]	Mainly DCQ	1,2,4,5	1,2,3,4,5,6
NWCS[123]	Other	1,2,3,4	3,6
POLS[111]	Other	1,4	1,3,4,5,6
Still Working[114]	Other	4,5	1,2,4,5,6

*JCQ = Job Content Questionnaire; DCQ = Demand control questionnaire; Mainly JCQ/Mainly DCQ = minor modifications from the original questionnaire; Other = job strain scale with proxy items.
**Demand items: 1. Working very fast; 2. Working very hard/intensively; 3. No excessive amount of work/too much effort; 4. Enough time;
5. Conflicting demands
†Control items: 1. Learn new things; 2. High level of skill; 3. Creativity/initiative; 4. Repetitive work; 5. A lot of say/what to do; 6. Little freedom/how to do

High correlation was found when the complete five-item demands scale and the partial demands scales with at least three items were compared. All the correlation coefficients were ≥0.94 when the partial scale consisted of four items, compared with ≥0.90 when it consisted of three items. Correlation was lower when the partial scale only had two items, but the coefficients were still at least 0.76. (Table 7)

The results were similar for the control scale, for which the complete scale consisted of six items and the partial scales of five or two items within these studies. The coefficients were very high ($r \geq 0.96$) when the partial scale consisted of five items, and compared to the complete scale; they were slightly lower, but still at least 0.81, when the partial scale only had two items. (Table 7)

Sensitivity, specificity and Kappa statistics were calculated to examine the agreement between definitions of job strain based on complete and partial job-demands and job-control scales. When only one item was missing from either scale, the agreement was very good ($\kappa > 0.80$ and sensitivity ≥ 0.74). When three job-demand items and all six control items were used to define job strain the agreement was at least good ($\kappa \geq 0.68$), as it was with one exception for job-strain definitions based on only two demand items but all six control items. Most of the Kappa statistics were at least good ($\kappa > 0.60$) when both scales had one or more items missing, although the agreement was moderate ($\kappa > 0.54$) in some comparisons. More missing items led to decreased sensitivity. (Table 8)

Table 7. Pearson product-moment correlation coefficients (r) and 95% confidence intervals (95% CI) between the complete psychological job-demands and job-control scales vs. the shorter versions (adapted from Sub-study I)

Scale	**Correlation coefficient**
Job Demands*	**Range**
Complete scale vs. B (4 items)	0.95-0.98
Complete scale vs. C (4 items)	0.94-0.96
Complete scale vs. D (3 items)	0.90-0.93
Complete scale vs. E (3 items)	0.90-0.93
Complete scale vs. F (2 items)	0.84-0.88
Complete scale vs. G (2 items)	0.76-0.82
Job Control**	
Complete scale vs. B (5 items)	0.97-0.98
Complete scale vs. C (5 items)	0.96-0.98
Complete scale vs. D (5 items)	0.97-0.98
Complete scale vs. E (5 items)	0.96-0.98
Complete scale vs. F (2 items)	0.81-0.87

*Abbreviated job-demands items of the complete scale: 1. "Work very fast"; 2."Work very hard/intensively"; 3. " No excessive work /Too much effort "; 4. "Enough time"; 5. "Conflicting demands". Version B includes items 1, 2, 4, 5; version C items 1, 2, 3, 4; version D items 2, 3, 4; version E items 1, 4, 5; version F items 1, 4; and version G items 4, 5.

**Abbreviated job-control items of the complete scale: 1. "Learn new things"; 2. "High level of skill"; 3. "Require creativity/initiative"; 4. "Repetitive work"; 5. "A lot of say"/"Deciding what to do"; 6. "Deciding how".

Version B includes items: 1,2,4,5,6; version C items: 1,2,3,4,6; version D items:1,3,4,5,6; version E items: 1,2,3,4,5; and version F items: 3,6.

Table 8. The agreement between definitions of job strain based on complete vs. partial scales (adapted from Sub-study I)

Job strain Version of partial scales*	Sensitivity Range	Specificity Range	Kappa Range
Complete demands and control scale vs. complete demands and partial control scale			
Demands version A, control version C (5 items)	0.85-0.97	0.95-1.00	0.81-0.90
Complete demands and control scale vs. partial demands and complete control scale			
Demands version B (4 items), control version A	0.74-0.98	0.96-1.00	0.83-0.93
Demands version C (4 items), control version A	0.75-0.96	0.96-1.00	0.82-0.87
Demands version D (3 items), control version A	0.56-0.92	0.96-1.00	0.68-0.86
Demands version E (3 items), control version A	0.61-0.91	0.95-1.00	0.69-0.86
Demands version F (2 items), control version A	0.46-0.70	0.97-0.99	0.58-0.77
Complete demands and control scale vs. partial demands and partial control scale			
Demands version C (4 items), control version F (2 items)	0.58-0.78	0.93-0.97	0.58-0.68
Demands version E (3 items), control version E (5 items)	0.45-0.78	0.95-0.99	0.55-0.76
Demands version F (2 items), control version D (5 items)	0.45-0.66	0.93-0.99	0.54-0.71
Demands version G (2 items), control version B (5 items)	0.43-0.73	0.94-0.99	0.54-0.70

*Abbreviated items of the complete demands scale (version A): 1. "Work very fast"; 2. "Work very hard/intensively"; 3. "Too much effort/No excessive work"; 4. "Enough time"; 5. "Conflicting demands". Version B includes items 1, 2, 4, 5; version C items 1, 2, 3, 4; version D items 2, 3, 4; version E items 1, 4, 5; version F items 1, 4; and version G items 4, 5.

Abbreviated items of the complete control scale (version A): 1. "Learn new things"; 2. "High level of skill"; 3. "Require creativity/initiative"; 4. "Repetitive work"; 5. "A lot of say"/"Deciding what to do"; 6. "Deciding how". Version B includes items: 1,2,4,5,6; version C items: 1,2,3,4,6; version D items:1,3,4,5,6; version E items: 1,2,3,4,5; and version F items: 3,6.

6.3 The association between job strain and BMI

Data from 13 European cohort studies (N=161 746) was used in Sub-study II to test the association between job strain and BMI, and four of these (Belstress, FPS, HeSSup and Whitehall II) provided repeated data on job strain and BMI measures with a median follow-up of four years. Table 9 lists the characteristics of the participants in the cohorts.

Slightly more than half (53.4%) of the participants covered in the cross-sectional data were of normal weight, whereas 1.3 per cent were underweight, 35 per cent overweight, 8.4 per cent obese class I, and 1.9 per cent obese classes II and III combined. Seventeen per cent of them had job strain. A U-shaped cross-sectional association was found between job strain and the BMI categories. Weight gain and weight loss were both associated with the onset of job strain. However, the associations were relatively small.

Table 9. The characteristics of the participants in the 13 cohort studies included in Sub-study II

Study (country)	Baseline year	Number of participants	Women (%)	Mean age (years)	Mean BMI (kg/m^2)	Job strain (%)
FPS (Finland)[105]	2000–2002	46 933	81	44.6	25.0	16
POLS (the Netherlands)[111]	1997–2002	23 836	41	38.3	24.4	16
Belstress (Belgium)[101]	1994–1998	20 983	23	45.5	26.1	19
HeSSup (Finland)[107]	1998	16 355	55	39.6	24.9	17
Gazel (France)[106]	1997	11 259	28	50.3	25.4	14
SLOSH (Sweden)[113]	2006 and 2008	10 698	54	47.6	25.4	20
Whitehall II (UK)[115]	1985–1988	10 262	33	44.4	24.6	14
WOLF S (Sweden)[117]	1992–1995	5643	43	41.5	24.6	16
DWECS (Denmark)[104]	2000	5523	46	41.8	24.6	22
WOLF N (Sweden)[116]	1996–1998	4692	16	44.1	26.2	13
IPAW (Denmark)[109]	1996–1997	1965	66	41.3	24.2	17
HNR (Germany)[108]	2000–2003	1823	41	53.4	27.4	12
PUMA (Denmark)[112]	1999–2000	1774	82	42.6	24.5	15
Total	**1985–2008**	**161 746**	**51**	**43.7**	**25.1**	**17**

6.3.1 Cross-sectional associations between job strain and obesity

In the age- and sex-adjusted model the risk of having job strain was the lowest among the normal-weight participants, and the highest among the underweight and obese groups. Compared to those who were of normal weight, the odds ratio was 1.12 (95% CI 1.01-1.25) for the underweight, 1.07 (95% CI 1.01-1.12) for the overweight, 1.19 (95% CI 1.13-1.25) for the class-I obese and 1.30 (95% CI 1.16-1.46) for the combined classes Ⅱ and Ⅲ obesity groups. Some attenuation in the effect estimates was noted after adjustment for SES, but the values remained statistically significant for both obesity categories. (Table 10)

Interactions were tested for the BMI categories and sex or age group (>50 vs. ≤50 years) in the pooled dataset, but no significant interactions were found (P for interaction was 0.36 for age and 0.35 for sex). The measurement method (self-reported vs. measured height and weight) was also examined as a possible source of heterogeneity. The analyses were thus run stratified by measurement method, but the results remained largely unchanged.

Table 10. Summary estimates for the association between the BMI categories and high job strain (adapted from Sub-study II)

BMI category	Number of participants	Odds ratio	95% CI
Adjustment for age and sex			
Underweight	2149	1.12	1.01-1.25
Normal weight	86 429	1.00	Reference
Overweight	56 572	1.07	1.01-1.12
Obese, class I	13 523	1.19	1.13-1.25
Obese, class Ⅱ-Ⅲ	3073	1.30	1.16-1.46
Adjustment for age, sex and SES			
Underweight	2149	1.12	1.00-1.25
Normal weight	86 429	1.00	Reference
Overweight	56 572	1.01	0.96-1.06
Obese, class I	13 523	1.07	1.02-1.12
Obese, class Ⅱ-Ⅲ	3073	1.14	1.01-1.28

6.3.2 Longitudinal associations between job strain and obesity

Baseline job strain was not associated with obesity at follow-up regardless of follow-up job strain. Furthermore, a change in BMI during follow-up was not associated with baseline job-strain status among initially non-obese participants. However, new exposure to job strain during follow-up was associated with incident obesity at follow-up (OR=1.18, 95% CI 1.02-1.36). (Table 11) This relationship was similar within each SES category.

Table 11. Age-, sex- and SES-adjusted longitudinal associations between job strain and incident obesity among non-obese participants in four studies based on repeated measurements

	N of participants (number/% of cases) *	Obesity at follow-up OR (95% CI)
Job strain at baseline		
No	35 715 (1748/4.9)	1.00 (reference)
Yes	6507 (336/5.2)	0.99 (0.88–1.12)
Job strain at baseline and at follow-up		
No and no	31 768 (1518/4.8)	1.00 (reference)
No and yes	3947 (230/5.8)	1.18 (1.02–1.36)
Yes and no	3796 (204/5.4)	1.06 (0.92–1.24)
Yes and yes	2711 (132/4.9)	0.95 (0.79–1.14)

*Participants who were of normal weight or overweight at baseline.

Reverse causation was examined among participants without job strain at baseline, but the BMI category at baseline was not associated with incident job strain. However, incident obesity was associated with an elevated risk (OR=1.18, 95% CI 1.02-1.36) of job strain at follow-up, a relationship that was also observed within each SES category. Furthermore, weight loss from obese to non-obese was associated with an increased risk of incident job strain when compared with the non-obese at both baseline and follow-up (OR=1.31, 95% CI 1.03-1.68). (Table 12)

Table 12. Age-, sex- and SES-adjusted longitudinal associations between body mass index (BMI) categories and job strain at follow-up among participants without job strain at baseline in four studies with repeated measurements (adapted from Sub-study II)

		N of participants (number/% of cases)	Job strain at follow-up OR (95% CI)
BMI category at baseline			
	Underweight	446 (54/12.1)	1.05 (0.79–1.41)
	Normal weight	22 701 (2488/11.0)	1.00 (reference)
	Overweight	13 014 (1459/11.2)	1.04 (0.97–1.12)
	Obese	3809 (458/12.0)	1.08 (0.96–1.20)
Obesity at baseline and at follow-up			
	No and no	34 412 (3771/11.0)	1.00 (reference)
	No and yes	1749 (230/13.2)	1.18 (1.02–1.36)
	Yes and no	551 (77/14.0)	1.31 (1.03–1.68)
	Yes and yes	3258 (381/11.7)	1.03 (0.92–1.15)

6.4 The association between job strain and physical inactivity

In Sub-study Ⅲ, individual-level data from 14 European cohort studies (N=170 162) was combined to allow examination of the association between job strain and leisure-time physical inactivity. Six of the cohort studies (Belstress, FPS, HeSSup, SLOSH, Whitehall Ⅱ and WOLF N) provided prospective data with a follow-up time of between two and nine years. Table 13 lists the characteristics of the study population. Job strain was divided into four categories and thus high strain was compared to low-strain in the analyses. The prevalence of leisure-time physical inactivity varied between seven and 38 per cent, and was 21 per cent in the total sample. The participants with high-strain jobs had elevated odds for physical inactivity in the cross-sectional analyses, and they also had elevated odds for becoming physically inactive during the follow-up.

Table 13. The characteristics of the study population in Sub-study III

Study	Number of participants	Mean age (years)	Female (%)	High strain (%)	Physical inactivity N (%)
FPS[105]	46 588	44.6	81	16	9 360 (20)
POLS[111]	24 753	38.3	41	16	4 669 (19)
Belstress[101]	20 397	45.4	23	19	4 527 (22)
HeSSup[107]	16 339	39.6	56	18	3 601 (22)
Gazel[106]	10 628	50.3	27	14	4 001 (38)
SLOSH[113]	10 853	47.6	54	20	2 072 (19)
Whitehall II[115]	10 133	44.4	33	14	1 652 (16)
Still Working[114]	8 969	40.8	23	15	1 748 (19)
WOLF S[117]	5 651	41.5	43	16	1 321 (23)
DWECS[104]	5 565	41.8	47	22	841 (15)
WOLF N[116]	4 686	44.1	17	13	1 254 (27)
IPAW[109]	1 965	41.2	66	18	151 (8)
HNR[108]	1 829	53.4	41	12	226 (12)
PUMA[112]	1 806	42.6	82	15	130 (7)

6.4.1 Cross-sectional associations between job strain and physical inactivity

Participants with high-strain jobs were more likely to be physically inactive than those with low-strain jobs (age- and sex-adjusted OR =1.36, 95% CI 1.25-1.48). Additional adjustment for SES and smoking only slightly attenuated this association (OR =1.26, 95% CI 1.15-1.38). The association was further studied when the data were stratified by sex, age, SES and smoking. The odds for physical inactivity turned out to be elevated among participants with high-strain jobs compared to those with low-strain jobs across all the studied subgroups (Table 14).

This analysis was repeated comparing individuals with job strain to all participants without job strain (including those with active, passive and low-strain jobs). The elevated risk from this approach was very similar, if not a little stronger: the age- and sex-adjusted odds ratio was 1.43 (95% CI: 1.36-1.51), and the age-, sex- and SES-adjusted odds ratio was 1.34 (95% CI: 1.26, 1.41).

Table 14. Cross-sectional associations between high job strain (compared to low strain) and leisure-time physical inactivity in the subgroups (adapted from Sub-study III)

Subgroup	Prevalence (%) of inactivity	OR (95% CI)*
All	25	1.32 (1.27-1.38)
Men	27	1.36 (1.28-1.44)
Women	24	1.28 (1.21-1.35)
Age <50 years	23	1.30 (1.23-1.37)
Age ≥50 years	28	1.34 (1.25-1.43)
Low SES	29	1.31 (1.22-1.41)
Intermediate SES	23	1.33 (1.26-1.41)
High SES	20	1.31 (1.16-1.47)
Never smokers	23	1.41 (1.32-1.50)
Ex-smokers	22	1.25 (1.17-1.35)
Current smokers	32	1.29 (1.20-1.40)

6.4.2 Longitudinal associations between job strain and physical inactivity

Prospective analyses restricted to participants who were physically active at baseline revealed that the odds of becoming physically inactive during the follow-up were 21-per-cent higher among those with baseline job strain compared to those with low baseline strain (OR=1.21, 95% CI 1.11-1.32) (Table 15). When the analysis was restricted to participants who were physically inactive at baseline, no clear associations were found between baseline work characteristics and becoming physically active at follow-up. However, physical inactivity at baseline was associated with elevated odds of having a high-strain job at follow-up. (Table 16)

Table 15. Age-, sex-, SES- and smoking-adjusted longitudinal associations between work characteristics at baseline and leisure-time physical activity or inactivity at follow-up (adapted from Sub-study III)

Baseline population Exposure at baseline	**N**	**Odds Ratio (95% CI)**	**N (%) of cases at follow-up**
Physically active at baseline		**Outcome at follow-up: Physical inactivity**	
Low strain	14 551	1 (reference)	1685 (12)
Passive	11 973	1.20 (1.11 - 1.30)	1806 (15)
Active	12 334	1.07 (0.99 - 1.15)	1483 (12)
High strain	7059	1.21 (1.11 - 1.32)	1049 (15)
Physically inactive at baseline		**Outcome at follow-up: Physical activity**	
Low strain	2861	1 (reference)	1416 (49)
Passive	3432	1.00 (0.90 - 1.11)	1634 (48)
Active	2545	1.10 (0.98 - 1.22)	1315 (52)
High strain	1970	0.98 (0.87 - 1.10)	946 (48)

Table 16. Age-, sex-, SES- and smoking-adjusted longitudinal associations between leisure-time physical activity and inactivity at baseline and work characteristics at follow-up (adapted from Sub-study III)

Baseline population Exposure at baseline	**N**	**Odds Ratio (95% CI)**	**N (%) cases at follow-up**
No high strain at baseline		**Outcome at follow-up: High strain job**	
Physically active	38 868	1 (reference)	3847 (10)
Physically Inactive	8838	1.15 (1.07 - 1.24)	1039 (12)
No active jobs at baseline		**Outcome at follow-up: Active job**	
Physically active	33 583	1 (reference)	5595 (17)
Physically inactive	8263	0.89 (0.83 - 0.96)	1150 (14)
No passive jobs at baseline		**Outcome at follow-up: Passive job**	
Physically active	33 954	1 (reference)	4763 (14)
Physically inactive	7376	1.12 (1.04 - 1.20)	1196 (16)
No low strain at baseline		**Outcome at follow-up: Low strain job**	
Physically active	31 376	1 (reference)	6881 (22)
Physically inactive	7947	0.89 (0.84 - 0.95)	1549 (19)

6.5 The association between job strain and other cardiac risk factors

Cross-sectional, individual level data from eight studies (N=47 045) was used to examine the associations between job strain and cardiovascular-disease risk factors. The mean age of the participants was 45.1 years and 29 per cent of them were women (Table 17). The cardiovascular-disease risk factors examined were diabetes, blood pressure, pulse pressure, blood lipids, smoking, alcohol consumption, physical inactivity, obesity and overall cardiovascular-disease risk, calculated in accordance with the Framingham cardiovascular-disease-risk score comprising age, total and HDL cholesterol, systolic blood pressure, hypertensive medication use, smoking and diabetes. High overall risk was defined as a Framingham score of 20 per cent or higher.

Table 17. Characteristics of the participants in Sub-study IV

Study	Baseline	N	Mean age (years)	Women (%)	Job strain (%)
KORA S1[110]	1984-1985	2460	42.3	35.1	483 (19.6)
KORA S2[110]	1989-1990	2370	42.3	37.8	417 (17.6)
Whitehall II[115]	1991-1993	7070	48.8	30.7	959 (13.6)
WOLF S[117]	1992-1995	5654	41.5	43.3	917 (16.2)
Belstress[101]	1994-1998	20 692	45.4	23.7	3900 (18.9)
KORA S3[110]	1994-1995	2345	42.6	40.6	372 (15.9)
WOLF N[116]	1996-1998	4678	44.0	16.7	599 (12.8)
HNR[108]	2000-2003	1776	53.3	41.4	217 (12.2)
Total	1984-2003	47 045	45.1	29.2	7864 (16.7)

Job strain was strongly linked to adverse lifestyle factors and diabetes, but its association with biological risk factors was minimal. An elevated association with the Framingham risk score was found, attributable to higher prevalences of smoking, physical inactivity and diabetes among participants with job strain.

Table 18 presents the associations between job strain and the risk factors, adjusted for age and sex. Compared to their counterparts with no strain, participants with job strain were more likely to be diabetic (OR=1.35, 95% CI 1.15-1.57), physically inactive (OR=1.43, 95% CI 1.36-1.51), smokers (OR=1.23, 95% CI 1.16-1.30) and obese (OR=1.19, 95% CI 1.11-1.28). With regard to alcohol consumption, they were more likely to be abstainers (OR=1.21, 95%

CI 1.13-1.30) and slightly more likely to be heavy users (OR=1.06, 95% CI 0.99-1.13). Further adjustment for SES had only a slight effect on the associations.

A high Framingham risk was more prevalent among those with job strain (OR=1.19, 95% CI 1.08-1.31), but this association was only attributable to components of diabetes and lifestyle factors given that it was eliminated following adjustment for physical inactivity, smoking and diabetes (OR=1.03, 95% CI 0.92-1.16).

The analyses adjusted for age, sex and SES revealed no associations between job strain and systolic or diastolic blood pressure, pulse pressure, cholesterol or triglyceride concentrations. Hypertension was equally prevalent among participants with or without job strain. The HDL cholesterol and cholesterol ratios were borderline statistically significant in the analyses adjusted only for age and sex, but the clinical differences in mean values were negligible.

The robustness of the association between job strain and diabetes was further examined in multivariable adjusted analyses. The additional adjustment for smoking, alcohol consumption, physical inactivity and obesity did not attenuate the association very much – indicating that it was not due to lifestyle factors. Moreover, the association was similar among men and women (age- and SES-adjusted OR=1.21, 95% CI 1.00-1.46 among men and OR=1.48, 95% CI 1.12-1.97 women), and the interaction between sex and job strain was not significant (p=0.18), either. Excluding shift workers did not change the association very much, but it became statistically non-significant (OR=1.20, 95% CI 0.99-1.45).

Table 18. The age- and sex-adjusted association between job strain and lifestyle and biological risk factors (adapted from Sub-study IV)

		Prevalence (%)		
	Total N	**No strain**	**Job strain**	**Odds ratio (95% CI)**
Lifestyle risk factors				
Obesity	46 891	13.7	15.7	1.19 (1.11, 1.28)
Physical inactivity	46 395	31.7	38.7	1.43 (1.36, 1.51)
Smoking	46 553	26.6	30.7	1.23 (1.16, 1.30)
Non-drinking (alcohol)	46 482	16.5	19.3	1.21 (1.13, 1.30) ‡
High alcohol use	46 482	21.6	21.6	1.06 (0.99, 1.13) ‡
Overall cardiovascular risk				
Framingham risk ≥20 points	45 428	9.6	9.9	1.19 (1.08, 1.31)
Biological risk factors				
Diabetes	46 510	2.2	2.8	1.35 (1.15, 1.57)
Hypertension	47 045	30.4	30.1	0.99 (0.94, 1.05)
		Mean (SE)		**Mean difference (95% CI)**
Systolic blood pressure, mmHg*	44 106	126.8 (1.6)	126.8 (1.6)	0.01 (-0.35, 0.38)
Diastolic blood pressure, mmHg*	44 104	79.5 (1.1)	79.5 (1.1)	-0.04 (-0.28, 0.21)
Pulse pressure, mmHg *	44 104	47.3 (1.2)	47.3 (1.2)	0.05 (-0.21, 0.31)
Total cholesterol, mmol/l †	45 776	5.87 (0.1)	5.89 (0.1)	0.01 (-0.01, 0.04)
HDL, mmol/l †	45 728	1.42 (0.01)	1.41 (0.01)	-0.01 (-0.02, -0.00)
Cholesterol ratio †	45 723	4.5 (0.1)	4.6 (0.1)	0.04 (0.00, 0.09)
Triglycerides, mmol/l †	18 858	1.4 (0.1)	1.4 (0.1)	0.01 (-0.01, 0.04)

*Participants not using antihypertensive medication.

†Participants not using lipid-lowering medication.

‡Compared to moderate drinkers only.

Table 19. The baseline characteristics of eligible participants in Sub-study V

Study	Method for diabetes diagnosis*	Country	Baseline	Number of participants	Percentage of women	Number (%) of participants with job strain	Mean age at baseline (years)	Person-years	Number of new type 2 diabetes cases (incidence per 10 000 person-years)
COPSOQ-I[102]	2	Denmark	1997	1758	49	358 (20)	40.7	20 467	44 (21.5)
COPSOQ-II[103]	2	Denmark	2004-05	3341	53	475 (14)	42.6	16 575	18 (10.9)
DWECS[104]	2	Denmark	2000	5522	47	1232 (22)	41.8	48 659	63 (12.9)
FPS[105]	3	Finland	2000	46 356	81	7529 (16)	44.5	444 925	1175 (26.4)
Gazel[106]	4	France	1997	10 882	28	1572 (14)	50.2	139 092	732 (52.6)
HeSSup[107]	3	Finland	1998	16 127	56	2824 (18)	39.5	112 026	129 (11.5)
IPAW[109]	2	Denmark	1996-97	1988	66	346 (17)	41.1	25 269	56 (22.2)
PUMA[112]	2	Denmark	1999-2000	1831	83	276 (15)	42.6	18 246	24 (13.2)
SLOSH[113]	2	Sweden	2006, 2008	10 644	54	2089 (20)	47.5	48 625	43 (8.8)
Still Working[114]	3	Finland	1986	9079	23	1419 (16)	40.9	191 416	730 (38.1)
Whitehall II[115]	1	UK	1991-93	7082	30	946 (13)	48.8	89 430	558 (62.4)
WOLF N[116]	2	Sweden	1996-98	4605	17	587 (13)	43.9	53 311	48 (9.0)
WOLF S[117]	2	Sweden	1992-95	5593	43	907 (16)	41.4	80 781	83 (10.3)
Total			**1986-2008**	**124 808**	**57**	**20 560 (16)**	**44.1**	**1 288 822**	**3703 (28.7)**

*1 = Repeated oral glucose-tolerance tests complemented by self-report
2 = Mortality and hospitalization registers
3 = Special reimbursement register, mortality and hospitalization registers
4 = Self-report based on annual surveys and mortality register

6.6 The association between job strain and incident diabetes

Individual participant data from 13 European cohort studies (N=124 808) was used to examine the association between job strain and incident type 2 diabetes. A total of 3,703 cases of incident diabetes appeared during the mean follow-up time of 10.3 years. Table 19 lists the baseline characteristics of the participants.

Table 20 shows the cross-sectional associations between job strain and diabetes with different adjustments (from Sub-study IV). The adjustments did not affect the estimates very much, indicating that the association between job strain and prevalent diabetes was robust.

Table 20. Multivariable adjusted associations between job strain and diabetes (N=44 818 in all models, adapted from Sub-study IV)

Adjustment	**Odds ratio for prevalent diabetes (95% CI)**
Age, sex, SES	1.33 (1.13 - 1.56)
Age, sex, SES, smoking	1.33 (1.13 - 1.56)
Age, sex, SES, alcohol consumption	1.31 (1.12 - 1.54)
Age, sex, SES, physical activity	1.30 (1.11 - 1.52)
Age, sex, SES, obesity	1.31 (1.12 - 1.54)
All above	1.28 (1.10 - 1.51)

Job strain turned out to be a risk factor for incident diabetes in men and women independently of the lifestyle factors. The age-, sex- and SES-adjusted hazard ratio for job strain compared to no strain was 1.15 (95% CI 1.06-1.25). The association was similar among men (HR=1.19, 95% CI 1.06-1.34) and women (HR=1.13, 95% CI 1.00-1.28), and among participants under the age of 50 (HR=1.13, 95% CI 0.99-1.28) and 50 years or older (HR=1.16, 95% CI 1.04-1.31). Following additional adjustment for lifestyle factors (BMI category, physical inactivity, smoking and alcohol consumption) the hazard ratio was 1.11 (95% CI 1.00-1.23), and after further adjustment for biological risk markers such as hypertension or blood lipid values the risk was HR=1.12 (95% CI 0.99-1.26). Furthermore, the risk was not attenuated when

events during the first three years were excluded (HR=1.15, 95% CI 1.05-1.27), indicating no evidence of reverse causation.(Table 21)

All individual lifestyle risk factors (obesity, physical inactivity, smoking and heavy alcohol use) were associated with an increased diabetes risk, and the strongest association was with obesity. The dichotomous lifestyle factors were combined with job strain to examine the risk of diabetes within these categories. All the lifestyle factors were still associated with an elevated risk of diabetes, and job strain was associated with a similar excess risk of type 2 diabetes among participants exposed and unexposed to each lifestyle risk factor. (Table 22)

There was variation between the studies in terms of the methods used for the ascertainment of diabetes. However, the risk estimates were similar when the results were stratified by the ascertainment method. Only in one study was the diagnosis based on repeated measures of the oral glucose-tolerance test (HR=1.09, 95% CI 0.86-1.37, Whitehall II) or on annual self-reported information from the questionnaires complemented with information from the mortality registry (HR=1.08, 95% CI 0.88-1.33, Gazel): the most common method was hospitalisation and the mortality registries (8 studies, HR=1.35, 95% CI 1.05-1.74, COPSOQ-I, COPSOQ-II, IPAW, DWECS, PUMA, SLOSH, WOLF N and WOLF S), or drug-reimbursement records in addition to the hospitalisation and mortality records (3 studies HR=1.08, 95% CI 0.88-1.33, FPS, HeSSup, Still Working). (Table 21)

Table 21. The association of job strain with incident type 2 diabetes in relation to the study follow-up periods, outcome ascertainment and adjustments (adapted from Sub-study V)

	Diabetes cases	Participants	Studies	HR (95% CI)
Follow-up period:				
Full follow-up	3703	124 808	13	1.15 (1.06-1.25)
Cases with diabetes diagnosed during first 3 years excluded	3241	124 346	13	1.15 (1.05-1.27)
Method of diabetes ascertainment:				
Oral glucose tolerance test	558	7082	1	1.09 (0.86-1.37)
Hospitalization and mortality registries	379	35 282	8	1.35 (1.05-1.74)
Hospitalization, mortality and drug reimbursement registries	2034	71 562	3	1.15 (1.03-1.29)
Self-report and mortality register	732	10 882	1	1.08 (0.88-1.33)
Model adjusted for:				
Age, sex	3703	124 808	13	1.26 (1.16-1.37)
Age, sex, SES	3703	124 808	13	1.15 (1.06-1.25)
Age, sex, SES, BMI category	2833	111 984	11	1.12 (1.02-1.24)
Age, sex, SES, physical activity	3523	120 364	12	1.13 (1.03-1.23)
Age, sex, SES, smoking	3591	120 495	13	1.14 (1.04-1.24)
Age, sex, SES, alcohol consumption	3539	110 447	11	1.14 (1.04-1.25)
Age, sex, SES, lifestyle variables*	2599	95 921	10	1.11 (1.00-1.23)
Age, sex, SES, lifestyle variables*, biomarkers†	1889	88 174	8	1.12 (0.99-1.26)
Age, sex, SES, lifestyle variables*, biomarkers‡	638	16 168	3	1.08 (0.87-1.35)

*Lifestyle variables: BMI (6 categories), physical activity (3 categories), smoking (3 categories), alcohol consumption (4 categories).

† Self-reported hypertension or use of antihypertensive medication (FPS, HeSSup, SLOSH, IPAW, COPSOQ-II), self-reported elevated lipids (HeSSup), or measured systolic blood pressure, triglycerides and high-density lipoprotein cholesterol (Whitehall II, WOLF N, WOLF S)

‡ Systolic blood pressure, triglycerides and high-density lipoprotein cholesterol (Whitehall II, WOLF N, WOLF S)

Table 22. Associations of job strain with incident type 2 diabetes in healthy- and unhealthy-lifestyle subgroups (adapted from Sub-study V)

Exposure	Participants (events)	HR for incident diabetes (95% CI)
Obesity –job strain		
No – No	84 437 (1423)	1.00 (reference)
No – Yes	16 379 (286)	1.13 (0.99 -1.28)
Yes – No	9135 (904)	5.99 (5.49-6.53)
Yes – Yes	2033 (220)	7.22 (6.22-8.37)
Physical inactivity –job strain		
No – No	80 365 (1954)	1.00 (reference)
No – Yes	15 104 (395)	1.14 (1.02-1.27)
Yes – No	20 351 (948)	1.61 (1.48-1.74)
Yes – Yes	4544 (226)	1.83 (1.59-2.11)
Smoking –job strain		
No – No	78 855 (2167)	1.00 (reference)
No – Yes	14 811 (445)	1.13 (1.02-1.25)
Yes – No	21 865 (790)	1.45 (1.33-1.58)
Yes – Yes	4964 (189)	1.70 (1.46-1.98)
Heavy drinking –job strain		
No – No	86 891 (2631)	1.00 (reference)
No – Yes	16 670 (569)	1.14 (1.04-1.25)
Yes – No	5873 (287)	1.37 (1.21-1.55)
Yes – Yes	1013 (52)	1.76 (1.34-2.32)

7 DISCUSSION

7.1 Synopsis of the main findings

The study reported in this thesis is based on a large, multi-cohort dataset covering several European countries, which was used to examine the associations of job strain with type 2 diabetes and its biological and lifestyle-related risk factors. The study populations used in the different analyses comprised 47,000 to 170,000 participants. Pre-specified variable definitions were used to minimise bias attributable to post-hoc decisions.

A major step involved harmonising and validating the exposure of interest, in other words job strain, across the studies (Sub-study I). The contents of the job-strain questionnaires varied between cohorts: not all of the items from the original scales were available in all of the studies, and in some cases the data included proxy items instead of the original questions. Nonetheless, it was possible to obtain partial job-demands and job-control scales that correlated strongly with the complete scales. The agreement of the dichotomous job-strain measure was "good" or "very good" when at least one of the underlying two subscales was complete. Even if one or more of the items of the underlying scales were missing, the agreement ranged from "moderate" to "good". These findings indicate that the partial job-demands and job-control scales that were available for the cohorts were similar enough to be used in pooled analyses.

Pooled analyses across the cohort studies revealed a complex association between job strain and BMI, corresponding to a U-shaped cross-sectional relationship with an increased prevalence of individuals with job strain in both the underweight and obese categories. A strong dose-response association was observed across the obesity categories such that the higher the level of obesity, the higher was the prevalence of job strain. The longitudinal analyses revealed that changes in job strain and BMI category tended to co-occur. Weight gain and weight loss were related to the onset of job strain during follow-up. Moreover, the change from no job strain at baseline to job strain at follow-up was associated with a category change from obese to non-obese.

Job strain was also associated with elevated odds for physical inactivity, another major risk factor for diabetes. It was found in further analyses based on longitudinal data that among participants who were physically active at baseline, those who reported job strain at baseline had a higher risk of

becoming physically inactive during the follow-up. However, there was also support for a bidirectional association in that physical-activity level at baseline predicted changes in job strain. For example, the physically inactive participants with no job strain at baseline were more likely to move into a high-strain category than their physically active counterparts.

Further analyses of a wider set of risk factors, including smoking, alcohol consumption, lipid parameters, blood pressure, pulse pressure, and Framingham cardiovascular-disease-risk scores, revealed consistent links between job strain and adverse lifestyle factors. An elevated risk of a high (>20%) Framingham risk score was additionally noted among those with job strain, but this association was attributable to the higher prevalence of smoking, physical inactivity and diabetes among these participants. Contrary to common belief, no clinically relevant associations were found between job strain and lipid levels, blood or pulse pressure, or the prevalence of hypertension.

In clinical terms, the most important finding was the evidence indicating that job-strain status is a type-2-diabetes risk factor in men and women regardless of lifestyle factors. The association was observed in the entire dataset and the magnitude of the elevated risk was similar in subgroups defined by age or sex, thus supporting a non-confounded association. Further evidence for this was obtained from the finding that job strain was associated with a similar excess risk of type 2 diabetes among participants with and without unhealthy lifestyle factors: obesity, physical inactivity, smoking and heavy alcohol consumption. These findings support the hypothesis that job strain is an independent type-2-diabetes risk factor.

7.2 Comparisons with previous research on alternative measures of job strain

The IPD-Work harmonisation approach was applied in that five and six comparable items were chosen as the "complete" scales, with confirmation of their theoretical adequacy obtained from Professor Töres Theorell, one of the creators of the job-strain model. The complete scales thus provided a reference measurement from which to examine the validity of the partial versions available in the IPD-Work cohort studies for which the complete scales were not available. A few previous studies have also compared different versions of job-strain questionnaires,[135] but the approach differs substantially from that of the IPD-Work analyses. In an analysis of data from 682

participants in the JACE study, a 14-item JCQ (five demand and nine control items) was compared with the 11-item DCQ (five demand and six control items), and moderate agreement between median-based job-strain classifications was found. The investigators also attempted to improve the comparability of the scales by developing comparability-facilitating algorithms, as well as using regression models to convert them to the same scale. However, the agreement was not meaningfully improved by the transformations.[135]

Further comparisons have been conducted between the original and different lingual versions. For example, the Japanese version of the Job Content Questionnaire, which included a total of 31 items from the JCQ, was investigated in a sample of 1,126 employees working in a computer company and was found to be a reliable and valid instrument.[136] A further study based on the GAZEL cohort of 11,447 participants yielded evidence of the validity of the French version of the four JCQ scales including psychological demands, decision latitude, social support and physical demands.[137] Thus, our findings and those of the previous studies in combination support the notion that job strain can be assessed reliably using different measurement instruments, a prerequisite in approaches based on pooling data from multiple studies.

7.3 Comparisons with previous studies on job strain and diabetes risk factors

The IPD-Work meta-analyses of individual participant data revealed robust, positive cross-sectional, and some positive longitudinal associations between job strain and both BMI and physical inactivity, but the associations were relatively modest in terms of absolute effect size and were not necessarily causal.

The association between job strain and BMI was examined using BMI as both a dichotomous (obese versus non obese) and a categorical variable, including the categories underweight, normal weight and overweight, and two categories of obesity. BMI has been used in previous studies as a continuous measure, or has been classified into a categorical or dichotomous measure. A further difficulty with comparing the results from IPD-Work and other studies relates to the fact that previous research on the association between work stress and BMI has been based on various definitions of work stress.

In spite of this methodological heterogeneity, our findings support previous analyses indicating a bidirectional association between work stress and

BMI,[57,58] in other words that work stress might be related to weight gain in some individuals and weight loss in others. Furthermore, the direction of the effect may be dependent on sex, baseline BMI and other factors. These opposite effects may override each other and lead to a conclusion of no association if BMI is analysed as a continuous trait.

After our findings were published, Fujishiro and colleagues analysed longitudinal data from the Nurses' Health Study to see whether change in job strain was associated with change in BMI. They found that people reporting high job strain at least once reported a bigger increase in BMI than those who did not. However, the association between change in job-strain status and change in BMI was dependent on baseline BMI such that the greater the latter value, the greater was the BMI gain associated with constantly elevated job strain. Furthermore, weight gain was associated with changes in job-strain status, independently of baseline BMI. [138] These findings indicate a complex association between job strain and BMI that has not been replicated in other studies.

A systematic review and meta-analysis of stress and BMI, published in 2015[139], identified eight studies that fulfilled the inclusion criteria. No evidence of an overall association between job strain and the risk of weight gain was found in that review (pooled odds ratio for job strain compared with no job strain was 1.04 (95% CI: 0.99-1.09), nor was there consistent evidence to support an association between job strain and becoming obese (OR=1.00, 95% CI: 0.89-1.13). Similarly, a reduction in job strain was not associated with a lower obesity risk (OR=1.13, 95% CI 0.90-1.41). In line with our findings, these results, which were based to some extent on the same studies as used in Sub-study II, imply that job strain is not a major risk factor for obesity and thus is not a promising target for obesity prevention.

An earlier review, conducted in 2004, identified 10 studies relating job strain, job demands and job control to general or abdominal obesity. The results did not generally support an association between psychological workload and either overall or abdominal obesity. The only positive associations reported were weak, and the authors concluded that longitudinal studies were needed in the future. Given that this review considered only linear associations, it could not, by design, detect the kind of non-linear U-shaped associations between job strain and BMI observed in our analyses of the BMI categories. [140]

A further review of the association between work stress and health-risk behaviour, reported in 2006[141], identified a variety of definitions for work

stress, including the job-strain model and the components of job strain. According to those results, the association between the demand-control model and body weight was confirmed in four studies and partially confirmed in eight. However, ten studies reported no association between job strain, or any of its components, and body weight or weight change.

A meta-analysis of published studies on the association between stress and adiposity was reported in 2010.[142] Based on a total of 8,514 participants, it produced no clear evidence of a longitudinal association between job strain and BMI (correlation coefficient 0.014, 95% CI: -0.002-0.031, p=0.09). However, the analyses in the review were also limited to linear associations.

Evidence on the association between job strain and physical inactivity is much scarcer. To my knowledge, only one integrative review on the topic has been published, in 2014.[143] According to this review, the relationships between the four job-strain categories and physical activity are inconsistent, differ between men and women and vary between countries. However, high-strain jobs, compared to low-strain jobs, were quite consistently negatively associated with leisure-time physical activity or exercise, a result that is consistent with our conclusions. The findings of two recent studies are also consistent with the IPD Work results. First, a Brazilian cohort-based study (ELSA-Brasil), published in 2015, reported results from analyses stratified by sex, in which elevated odds ratios for physical inactivity were observed in men and women when job strain was compared with low job strain.[144] Second, the conclusion in a recent study conducted by Oshio and colleagues and published in 2016 was also concordant with the IPD Work result. The latter study was based on data from a Japanese occupational-cohort survey, and the odds ratio for physical inactivity was 22-per-cent higher among those with high-strain jobs and 17-per-cent higher for those with active jobs when compared with those with low-strain jobs.[145]

According to all this evidence, the association between job strain and BMI appears to be complicated, and the association between job strain and physical inactivity is less complicated. Nevertheless, both effects are, at best, quite small in magnitude. Furthermore, there is no strong evidence in these results to suggest that interventions to reduce job strain would be effective in reducing obesity on the population level. Intervention studies are required to confirm these findings, as well as to evaluate the relevance of job strain in relation to promoting physical activity.

7.4 Job strain and the risk of diabetes

The results from the IPD-Work analyses indicate that job strain is related to a small, but statistically significant and robust increase in the risk of both prevalent and incident diabetes. Previous studies on this issue were based on much smaller data sets, and they implied that job strain and diabetes were not inter-related, at least not among men,[91-98] although some positive associations were found among women.[91-94] Some of these results were combined in a review paper published in 2012, which concluded on the basis of a pooled analysis of four studies (total N = 92,485 that there was no association between high strain and the risk of diabetes.[100] However, when all the previous results were combined in a new analysis, a suggestion of an elevated risk among women, but not among men, was noted (Figure 2). The IPD-Work analyses, which were based on a 1.3-times bigger sample and a harmonised definition of job strain, revealed a similar association among men (HR=1.19, 95% CI 1.06-1.34) and women (HR=1.13, 95% CI 1.00-1.28). The previous analyses, which were based on much smaller data sets than the IPD-Work analyses, may have lacked the statistical power to detect such differences in risk. Our analyses were well powered, even for subgroup analyses. The elevated risk was noted both in the total sample and among the nine studied subgroups, supporting the possibility that the association may be causal. Most importantly, the risk was equally elevated among participants with and without unhealthy lifestyle factors such as obesity, physical inactivity, smoking, and heavy alcohol consumption.

Few studies on the association between job strain and incident type-2 diabetes have been published since the IPD Work results were revealed. Findings from the MONICA/KORA Augsburg cohort study were published in 2014, and reported an elevated risk of type 2 diabetes among those with high as opposed to low job strain.[146] A recent study based on middle-aged or older US workers and published in 2016, used longitudinal data to examine the association between job strain and incident type-2 diabetes: it reported an elevated disease risk among people with job strain.[147]

However, a systematic review and meta-analysis of prospective cohort studies, published in 2016, included results from seven studies, of which the IPD Work study was one.[92,94,96-98,122,146] The authors of the review concluded that a direct association between work-related stress and a type-2 diabetes risk could not be confirmed: it was only in a subgroup analysis among women that job strain turned out to be a risk factor for type 2 diabetes. These findings are in line with

those reported in Figure 2 of this thesis, but no difference was found in the association between men and women in the IPD Work analyses. Possible explanations for this discrepancy include the heterogeneity in the definitions of job strain and case-ascertainment, differences in the adjustments, or differences in the population related to ethnicity, for example.

7.5 Strengths and limitations

The main strengths of the studies analysed in this thesis include the utilisation of data from multiple independent cohort studies that together comprise a very large analytical sample, thereby providing a high level of statistical precision and generalizability. The generalizability of the findings is enhanced by the inclusion in the data of multiple populations from several European countries, and the various study settings with a pre-defined harmonised operational definition of the variables. A common concern in previous studies has been the use of heterogeneous definitions of exposure, which complicates the comparisons between the studies and increases the risk of selective reporting of the results. These caveats were largely avoided in the IPD-Work analyses given the use of predefined, carefully harmonised key variables.

The large dataset, including high numbers of participants across the entire BMI distribution, allowed us to conduct more refined analyses than has been possible thus far. Unlike other studies, ours allowed us to analyse underweight participants separately, and to distinguish stages of obesity. A further strength of the individual-participant meta-analysis of published and unpublished data is that it allowed us to examine publication bias and thereby determine whether this may have contributed to the overestimation of any associations in the literature-based meta-analyses.

The prospective design of Sub-studies Ⅱ, Ⅲ and V reduced the risk of reverse-causation bias. However, type 2 diabetes has a long subclinical phase, which increases the risk. We sought to minimise the bias by excluding the first three years of follow-up in Sub-study V. The risk estimate was not attenuated after this exclusion, indicating that reverse causation did not explain the observed association. However, further research is needed to allow examination of the impact of subclinical disease over a longer period before the onset of diabetes.

This work has some limitations. The original job-strain questionnaires were not applied in all of the participating studies, and no standardised procedure was followed when the original questionnaires were translated. Even after harmonisation of the variable, heterogeneity in the measurement of job strain

might have caused errors in the determination of exposure. In addition, most of the variables at baseline were based on questionnaire data, which is prone to errors due to subjectivity bias. This study focused on job strain, which is a widely studied form of work stress, but there are several other conceptualisations of work-related stress and stressors unrelated to work that were not taken into account in the analyses. It is possible that the cumulative effect of various sources of stress would have a stronger effect on the outcomes featured in this study.

A further limitation is the variation between the studies with regard to the ascertainment of incident type 2 diabetes. Only in one study (Whitehall II) was an oral glucose-tolerance test, the gold standard, administered repeatedly to all participants who had not already been diagnosed with diabetes over the follow-up period. Hence, this was the only study that was able to identify both diagnosed and undiagnosed diabetes. Other studies were based on health records and self-reports, and thus missed undiagnosed cases of type 2 diabetes. However, any resulting bias is likely to be small, given that stratification of the analyses by the method of ascertainment produced similar risk estimates. Moreover, I^2 statistics indicated that the method of outcome ascertainment was not a major source of heterogeneity between the studies. Furthermore, these analyses were not based on a systematic review. Finally, it is not possible to draw causal inferences because the data were not based on a randomised, controlled trial, which is the gold standard of study design.

7.6 Conclusions and implications for further research

This multi-cohort study shows that job strain is associated with an increased risk of diabetes and its risk factors, obesity and physical inactivity in particular. However, the associations, while robust, were relatively modest in magnitude, suggesting that intervention to reduce job strain might not be effective in combating the increasing incidence of diabetes on the population level.

Further research is needed. There is no standard intervention to alleviate job strain, and few intervention studies have been conducted to examine its reduction. Due to the nature of the exposure variable, the use of cluster-randomised, controlled trials to investigate the effect of a reduction in job strain, with work units or work places as the entity for randomisation, would be needed in the future to determine whether stress management could be an effective means of reducing adverse health outcomes in working populations. Although it may be difficult to obtain funding for very large

intervention studies, numerous small experiments would facilitate the accumulation of a reliable evidence base over time.

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REFERENCES

1. International Diabetes Federation. Updated Diabetes Atlas 2011, 5th ed. Brussels, 2011.
2. Canadian Diabetes Association Clinical Practice Guidelines Expert C, Goldenberg R, Punthakee Z. Definition, classification and diagnosis of diabetes, prediabetes and metabolic syndrome. *Can J Diabetes* 2013; 37 Suppl 1: S8-11.
3. Grundy SM, Benjamin IJ, Burke GL, et al. Diabetes and cardiovascular disease: a statement for healthcare professionals from the American Heart Association. *Circulation* 1999; 100(10): 1134-46.
4. Resnick HE, Howard BV. Diabetes and cardiovascular disease. *Annu Rev Med* 2002; 53: 245-67.
5. McCall AL. The impact of diabetes on the CNS. *Diabetes* 1992; 41(5): 557-70.
6. Stamler J, Vaccaro O, Neaton JD, Wentworth D. Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. *Diabetes Care* 1993; 16(2): 434-44.
7. Gu K, Cowie CC, Harris MI. Diabetes and decline in heart disease mortality in US adults. *Jama* 1999; 281(14): 1291-7.
8. Kannel WB, McGee DL. Diabetes and cardiovascular disease. The Framingham study. *Jama* 1979; 241(19): 2035-8.
9. Leibson CL, Rocca WA, Hanson VA, et al. Risk of dementia among persons with diabetes mellitus: a population-based cohort study. *Am J Epidemiol* 1997; 145(4): 301-8.
10. Ott A, Stolk RP, van Harskamp F, Pols HA, Hofman A, Breteler MM. Diabetes mellitus and the risk of dementia: The Rotterdam Study. *Neurology* 1999; 53(9): 1937-42.
11. Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis

for the Global Burden of Disease Study 2010. *Lancet* 2012; 380(9859): 2095-128.

12. Kahn SE, Hull RL, Utzschneider KM. Mechanisms linking obesity to insulin resistance and type 2 diabetes. *Nature* 2006; 444(7121): 840-6.

13. Pan XR, Li GW, Hu YH, et al. Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance. The Da Qing IGT and Diabetes Study. *Diabetes Care* 1997; 20(4): 537-44.

14. Tuomilehto J, Lindstrom J, Eriksson JG, et al. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med* 2001; 344(18): 1343-50.

15. Ohlson LO, Larsson B, Bjorntorp P, et al. Risk factors for type 2 (non-insulin-dependent) diabetes mellitus. Thirteen and one-half years of follow-up of the participants in a study of Swedish men born in 1913. *Diabetologia* 1988; 31(11): 798-805.

16. Ryden L, Standl E, Bartnik M, et al. Guidelines on diabetes, pre-diabetes, and cardiovascular diseases: executive summary. The Task Force on Diabetes and Cardiovascular Diseases of the European Society of Cardiology (ESC) and of the European Association for the Study of Diabetes (EASD). *Eur Heart J* 2007; 28(1): 88-136.

17. Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 2002; 346(6): 393-403.

18. Reis JP, Loria CM, Sorlie PD, Park Y, Hollenbeck A, Schatzkin A. Lifestyle factors and risk for new-onset diabetes: a population-based cohort study. *Ann Intern Med* 2011; 155(5): 292-9.

19. Karasek RA. Job demands, job decision latitude, and mental strain – implications for job redesign. *Administrative Science Quarterly* 1979; 24(2): 285-308.

20. Karasek R, Theorell T. Healthy work : stress, productivity, and the reconstruction of working life. New York: Basic Books; 1990.

21. Job Content Questionnaire, Recommended format. http://www.jcqcenter.org/.
22. Theorell T, Perski A, Akerstedt T, et al. Changes in job strain in relation to changes in physiological state. A longitudinal study. *Scand J Work Environ Health* 1988; 14(3): 189-96.
23. Jansen AS, Nguyen XV, Karpitskiy V, Mettenleiter TC, Loewy AD. Central command neurons of the sympathetic nervous system: basis of the fight-or-flight response. *Science* 1995; 270(5236): 644-6.
24. Schneiderman N, Ironson G, Siegel SD. Stress and health: psychological, behavioral, and biological determinants. *Annu Rev Clin Psychol* 2005; 1: 607-28.
25. Steptoe A, Hamer M, Chida Y. The effects of acute psychological stress on circulating inflammatory factors in humans: a review and meta-analysis. *Brain Behav Immun* 2007; 21(7): 901-12.
26. Selye H. A syndrome produced by diverse nocuous agents. *Nature* 1936; 138(32).
27. McEwen BS. Protective and damaging effects of stress mediators. *N Engl J Med* 1998; 338(3): 171-9.
28. McEwen BS, Stellar E. Stress and the individual. Mechanisms leading to disease. *Arch Intern Med* 1993; 153(18): 2093-101.
29. Chida Y, Steptoe A. Cortisol awakening response and psychosocial factors: a systematic review and meta-analysis. *Biol Psychol* 2009; 80(3): 265-78.
30. Kumari M, Shipley M, Stafford M, Kivimaki M. Association of diurnal patterns in salivary cortisol with all-cause and cardiovascular mortality: findings from the Whitehall II study. *J Clin Endocrinol Metab* 2011; 96(5): 1478-85.
31. Yanovski JA, Cutler GB, Jr. Glucocorticoid action and the clinical features of Cushing's syndrome. *Endocrinol Metab Clin North Am* 1994; 23(3): 487-509.
32. Bjorntorp P. Body fat distribution, insulin resistance, and metabolic diseases. *Nutrition (Burbank, Los Angeles County, Calif* 1997; 13(9): 795-803.
33. Incollingo Rodriguez AC, Epel ES, White ML, Standen EC, Seckl JR, Tomiyama AJ. Hypothalamic-pituitary-adrenal axis dysregulation and cortisol

activity in obesity: A systematic review. *Psychoneuroendocrinology* 2015; 62: 301-18.
34. Schorr M, Lawson EA, Dichtel LE, Klibanski A, Miller KK. Cortisol Measures Across the Weight Spectrum. *J Clin Endocrinol Metab* 2015; 100(9): 3313-21.
35. Bjorntorp P. Endocrine abnormalities of obesity. *Metabolism* 1995; 44(9 Suppl 3): 21-3.
36. Tabak AG, Herder C, Rathmann W, Brunner EJ, Kivimaki M. Prediabetes: a high-risk state for diabetes development. *Lancet* 2012; 379(9833): 2279-90.
37. Committee CDACPGE. Canadian Diabetes Association 2013 clinical practice guidelines for the prevention and management of diabetes in Canada. *Can J Diabetes* 2013; 37 Suppl 1: S1-212.
38. Raikkonen K, Matthews KA, Kuller LH. The relationship between psychological risk attributes and the metabolic syndrome in healthy women: antecedent or consequence? *Metabolism* 2002; 51(12): 1573-7.
39. Golden SH, Williams JE, Ford DE, et al. Depressive symptoms and the risk of type 2 diabetes: the Atherosclerosis Risk in Communities study. *Diabetes Care* 2004; 27(2): 429-35.
40. Unden AL, Orth-Gomer K, Elofsson S. Cardiovascular effects of social support in the work place: twenty-four-hour ECG monitoring of men and women. *Psychosom Med* 1991; 53(1): 50-60.
41. Nilsson PM, Nilsson JA, Hedblad B, Berglund G. Sleep disturbance in association with elevated pulse rate for prediction of mortality--consequences of mental strain? *J Intern Med* 2001; 250(6): 521-9.
42. Spiegel K, Leproult R, Van Cauter E. Impact of sleep debt on metabolic and endocrine function. *Lancet* 1999; 354(9188): 1435-9.
43. Golden SH, Williams JE, Ford DE, et al. Anger temperament is modestly associated with the risk of type 2 diabetes mellitus: the Atheroslcerosis Risk in Communities Study. *Psychoneuroendocrinology* 2006; 31(3): 325-32.
44. Chandola T, Brunner E, Marmot M. Chronic stress at work and the metabolic syndrome: prospective study. *BMJ* 2006; 332(7540): 521-5.

45. Everson-Rose SA, Meyer PM, Powell LH, et al. Depressive symptoms, insulin resistance, and risk of diabetes in women at midlife. *Diabetes Care* 2004; 27(12): 2856-62.
46. Ng M, Fleming T, Robinson M, et al. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 2014; 384(9945): 766-81.
47. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. *World Health Organization technical report series* 2000; 894: i-xii, 1-253.
48. Hubert HB, Feinleib M, McNamara PM, Castelli WP. Obesity as an independent risk factor for cardiovascular disease: a 26-year follow-up of participants in the Framingham Heart Study. *Circulation* 1983; 67(5): 968-77.
49. McLellan F. Obesity rising to alarming levels around the world. *Lancet* 2002; 359(9315): 1412.
50. Chan JM, Rimm EB, Colditz GA, Stampfer MJ, Willett WC. Obesity, fat distribution, and weight gain as risk factors for clinical diabetes in men. *Diabetes Care* 1994; 17(9): 961-9.
51. Colditz GA, Willett WC, Rotnitzky A, Manson JE. Weight gain as a risk factor for clinical diabetes mellitus in women. *Ann Intern Med* 1995; 122(7): 481-6.
52. Carroll KK. Obesity as a risk factor for certain types of cancer. *Lipids* 1998; 33(11): 1055-9.
53. Kouvonen A, Kivimaki M, Vaananen A, et al. Job strain and adverse health behaviors: the Finnish Public Sector Study. *J Occup Environ Med* 2007; 49(1): 68-74.
54. Heikkila K, Fransson EI, Nyberg ST, et al. Job strain and health-related lifestyle: findings from an individual-participant meta-analysis of 118,000 working adults. *Am J Public Health* 2013; 103(11): 2090-7.

55. Kouvonen A, Kivimaki M, Elovainio M, Virtanen M, Linna A, Vahtera J. Job strain and leisure-time physical activity in female and male public sector employees. *Prev Med* 2005; 41(2): 532-9.
56. Wardle J, Steptoe A, Oliver G, Lipsey Z. Stress, dietary restraint and food intake. *J Psychosom Res* 2000; 48(2): 195-202.
57. Hannerz H, Albertsen K, Nielsen ML, Tuchsen F, Burr H. Occupational factors and 5-year weight change among men in a danish national cohort. *Health Psychol* 2004; 23(3): 283-8.
58. Kivimaki M, Head J, Ferrie JE, et al. Work stress, weight gain and weight loss: evidence for bidirectional effects of job strain on body mass index in the Whitehall II study. *Int J Obes* 2006; 30(6): 982-7.
59. Kishi T, Elmquist JK. Body weight is regulated by the brain: a link between feeding and emotion. *Mol Psychiatry* 2005; 10(2): 132-46.
60. van den Berg TIJ, Elders LAM, de Zwart BCH, Burdorf A. The effects of work-related and individual factors on the Work Ability Index: a systematic review. *Occup Environ Med* 2009; 66(4): 211-20.
61. Kouvonen A, Kivimaki M, Cox SJ, Cox T, Vahtera J. Relationship between work stress and body mass index among 45,810 female and male employees. *Psychosom Med* 2005; 67(4): 577-83.
62. Ostry AS, Radi S, Louie AM, LaMontagne AD. Psychosocial and other working conditions in relation to body mass index in a representative sample of Australian workers. *BMC Public Health* 2006; 6: 53.
63. Brisson C, Larocque B, Moisan J, Vezina M, Dagenais GR. Psychosocial factors at work, smoking, sedentary behavior, and body mass index: a prevalence study among 6995 white collar workers. *J Occup Environ Med* 2000; 42(1): 40-6.
64. Eek F, Ostergren PO. Factors associated with BMI change over five years in a Swedish adult population. Results from the Scania Public Health Cohort Study. *Scand J Public Health* 2009; 37(5): 532-44.

65. Fernandez ID, Su H, Winters PC, Liang H. Association of workplace chronic and acute stressors with employee weight status: data from worksites in turmoil. *J Occup Environ Med* 2010; 52 Suppl 1: S34-41.
66. Hellerstedt WL, Jeffery RW. The association of job strain and health behaviours in men and women. *Int J Epidemiol* 1997; 26(3): 575-83.
67. Netterstrom B, Kristensen TS, Damsgaard MT, Olsen O, Sjol A. Job strain and cardiovascular risk-factors - a cross-sectional study of employed Danish men and women. *Br J Ind Med* 1991; 48(10): 684-9.
68. Shields M. Long working hours and health. *Health Rep* 1999; 11(2): 33-48(Eng); 37-55(Fre).
69. Ishizaki M, Nakagawa H, Morikawa Y, Honda R, Yamada Y, Kawakami N. Influence of job strain on changes in body mass index and waist circumference--6-year longitudinal study. *Scand J Work Environ Health* 2008; 34(4): 288-96.
70. Hu G, Tuomilehto J, Silventoinen K, Barengo NC, Peltonen M, Jousilahti P. The effects of physical activity and body mass index on cardiovascular, cancer and all-cause mortality among 47 212 middle-aged Finnish men and women. *Int J Obes* 2005; 29(8): 894-902.
71. Trolle-Lagerros Y, Mucci LA, Kumle M, et al. Physical activity as a determinant of mortality in women. *Epidemiology* 2005; 16(6): 780-5.
72. Sofi F, Capalbo A, Cesari F, Abbate R, Gensini GF. Physical activity during leisure time and primary prevention of coronary heart disease: an updated meta-analysis of cohort studies. *Eur J Cardiovasc Prev Rehabil* 2008; 15(3): 247-57.
73. Nocon M, Hiemann T, Muller-Riemenschneider F, Thalau F, Roll S, Willich SN. Association of physical activity with all-cause and cardiovascular mortality: a systematic review and meta-analysis. *Eur J Cardiovasc Prev Rehabil* 2008; 15(3): 239-46.
74. Gill JM, Cooper AR. Physical activity and prevention of type 2 diabetes mellitus. *Sports Med* 2008; 38(10): 807-24.
75. Monninkhof EM, Elias SG, Vlems FA, et al. Physical activity and breast cancer: a systematic review. *Epidemiology* 2007; 18(1): 137-57.

76. Voskuil DW, Monninkhof EM, Elias SG, et al. Physical activity and endometrial cancer risk, a systematic review of current evidence. *Cancer Epidemiol Biomarkers Prev* 2007; 16(4): 639-48.
77. Harriss DJ, Atkinson G, Batterham A, et al. Lifestyle factors and colorectal cancer risk (2): a systematic review and meta-analysis of associations with leisure-time physical activity. *Colorectal Dis* 2009; 11(7): 689-701.
78. Landsbergis PA, Schnall PL, Deitz DK, Warren K, Pickering TG, Schwartz JE. Job strain and health behaviors: results of a prospective study. *Am J Health Promot* 1998; 12(4): 237-45.
79. Lallukka T, Sarlio-Lahteenkorva S, Roos E, Laaksonen M, Rahkonen O, Lahelma E. Working conditions and health behaviours among employed women and men: the Helsinki Health Study. *Prev Med* 2004; 38(1): 48-56.
80. Yang X, Telama R, Hirvensalo M, et al. The benefits of sustained leisure-time physical activity on job strain. *Occup Med (Lond)* 2010; 60(5): 369-75.
81. Tsutsumi A, Kayaba K, Yoshimura M, et al. Association between job characteristics and health behaviors in Japanese rural workers. *Int J Behav Med* 2003; 10(2): 125-42.
82. Bennett GG, Wolin KY, Avrunin JS, et al. Does race/ethnicity moderate the association between job strain and leisure time physical activity? *Ann Behav Med* 2006; 32(1): 60-7.
83. Choi B, Schnall PL, Yang H, et al. Psychosocial working conditions and active leisure-time physical activity in middle-aged us workers. *Int J Occup Med Environ Health* 2010; 23(3): 239-53.
84. Wemme KM, Rosvall M. Work related and non-work related stress in relation to low leisure time physical activity in a Swedish population. *J Epidemiol Community Health* 2005; 59(5): 377-9.
85. Gimeno D, Elovainio M, Jokela M, De Vogli R, Marmot MG, Kivimaki M. Association between passive jobs and low levels of leisure-time physical activity: the Whitehall II cohort study. *Occup Environ Med* 2009; 66(11): 772-6.

86. Payne N, Jones F, Harris PR. The impact of job strain on the predictive validity of the theory of planned behaviour: an investigation of exercise and healthy eating. *Br J Health Psychol* 2005; 10(Pt 1): 115-31.

87. van Loon AJ, Tijhuis M, Surtees PG, Ormel J. Lifestyle risk factors for cancer: the relationship with psychosocial work environment. *Int J Epidemiol* 2000; 29(5): 785-92.

88. Tabak AG, Jokela M, Akbaraly TN, Brunner EJ, Kivimaki M, Witte DR. Trajectories of glycaemia, insulin sensitivity, and insulin secretion before diagnosis of type 2 diabetes: an analysis from the Whitehall II study. *Lancet* 2009; 373(9682): 2215-21.

89. Brotman DJ, Golden SH, Wittstein IS. The cardiovascular toll of stress. *Lancet* 2007; 370(9592): 1089-100.

90. Brunner E. Biology and health inequality. *PLoS Biol* 2007; 5(11): e267.

91. Leynen F, Moreau M, Pelfrene E, Clays E, De Backer G, Kornitzer M. Job stress and prevalence of diabetes: results from the Belstress study. *Arch Public Health* 2003; 61(1-2): 75-90.

92. Heraclides A, Chandola T, Witte DR, Brunner EJ. Psychosocial stress at work doubles the risk of type 2 diabetes in middle-aged women: evidence from the Whitehall II study. *Diabetes Care* 2009; 32(12): 2230-5.

93. Norberg M, Stenlund H, Lindahl B, Andersson C, Eriksson JW, Weinehall L. Work stress and low emotional support is associated with increased risk of future type 2 diabetes in women. *Diabetes Res Clin Pract* 2007; 76(3): 368-77.

94. Eriksson AK, van den Donk M, Hilding A, Ostenson CG. Work stress, sense of coherence, and risk of type 2 diabetes in a prospective study of middle-aged Swedish men and women. *Diabetes Care* 2013; 36(9): 2683-9.

95. Agardh EE, Ahlbom A, Andersson T, et al. Work stress and low sense of coherence is associated with type 2 diabetes in middle-aged Swedish women. *Diabetes Care* 2003; 26(3): 719-24.

96. Kawakami N, Araki S, Takatsuka N, Shimizu H, Ishibashi H. Overtime, psychosocial working conditions, and occurrence of non-insulin dependent

diabetes mellitus in Japanese men. *J Epidemiol Community Health* 1999; 53(6): 359-63.

97. Kroenke CH, Spiegelman D, Manson J, Schernhammer ES, Colditz GA, Kawachi I. Work characteristics and incidence of type 2 diabetes in women. *Am J Epidemiol* 2007; 165(2): 175-83.

98. Smith PM, Glazier RH, Lu H, Mustard CA. The psychosocial work environment and incident diabetes in Ontario, Canada. *Occup Med* 2012; 62(6): 413-9.

99. Heraclides AM, Chandola T, Witte DR, Brunner EJ. Work stress, obesity and the risk of type 2 diabetes: gender-specific bidirectional effect in the Whitehall II study. *Obesity (Silver Spring)* 2012; 20(2): 428-33.

100. Cosgrove MP, Sargeant LA, Caleyachetty R, Griffin SJ. Work-related stress and Type 2 diabetes: systematic review and meta-analysis. *Occup Med* 2012; 62(3): 167-73.

101. De Bacquer D, Pelfrene E, Clays E, et al. Perceived job stress and incidence of coronary events: 3-year follow-up of the Belgian Job Stress Project cohort. *Am J Epidemiol* 2005; 161(5): 434-41.

102. Kristensen TS, Hannerz H, Hogh A, Borg V. The Copenhagen Psychosocial Questionnaire--a tool for the assessment and improvement of the psychosocial work environment. *Scand J Work Environ Health* 2005; 31(6): 438-49.

103. Pejtersen JH, Kristensen TS, Borg V, Bjorner JB. The second version of the Copenhagen Psychosocial Questionnaire. *Scand J Public Health* 2010; 38(3 Suppl): 8-24.

104. Feveile H, Olsen O, Burr H, Bach E. Danish Work Environment Cohort Study 2005: From idea to sampling design. *Statistics in Transition* 2007; 8(3): 441-58.

105. Kivimäki M, Lawlor DA, Smith GD, et al. Socioeconomic Position, Co-Occurrence of Behavior-Related Risk Factors, and Coronary Heart Disease: the Finnish Public Sector Study. *Am J Public Health* 2007; 97(5): 874-9.

106. Goldberg M, Leclerc A, Bonenfant S, et al. Cohort profile: the GAZEL Cohort Study. *Int J Epidemiol* 2007; 36(1): 32-9.
107. Korkeila K, Suominen S, Ahvenainen J, et al. Non-response and related factors in a nation-wide health survey. *Eur J Epidemiol* 2001; 17(11): 991-9.
108. Stang A, Moebus S, Dragano N, et al. Baseline recruitment and analyses of nonresponse of the Heinz Nixdorf Recall Study: identifiability of phone numbers as the major determinant of response. *Eur J Epidemiol* 2005; 20(6): 489-96.
109. Nielsen M, Kristensen T, Smith-Hansen L. The Intervention Project on Absence and Well-being (IPAW): design and results from the baseline of a 5-year study. *Work and Stress* 2002; 16: 191-206.
110. Holle R, Happich M, Lowel H, Wichmann HE. KORA--a research platform for population based health research. *Gesundheitswesen* 2005; 67 Suppl 1: S19-25.
111. de Groot W, Dekker R. The Dutch System of Official Social Surveys. Mannheim: Mannheim Centre for European Social Research, 2001.
112. Borritz M, Rugulies R, Bjorner JB, Villadsen E, Mikkelsen OA, Kristensen TS. Burnout among employees in human service work: design and baseline findings of the PUMA study. *Scand J Public Health* 2006; 34(1): 49-58.
113. Hasson D, Theorell T, Westerlund H, Canlon B. Prevalence and characteristics of hearing problems in a working and non-working Swedish population. *J Epidemiol Community Health* 2010; 64(5): 453-60.
114. Väänänen A, Murray M, Koskinen A, Vahtera J, Kouvonen A, Kivimäki M. Engagement in cultural activities and cause-specific mortality: prospective cohort study. *Prev Med* 2009; 49(2-3): 142-7.
115. Marmot MG, Smith GD, Stansfeld S, et al. Health inequalities among British civil servants: the Whitehall II study. *Lancet* 1991; 337(8754): 1387-93.
116. Alfredsson L, Hammar N, Fransson E, et al. Job strain and major risk factors for coronary heart disease among employed males and females in a Swedish study on work, lipids and fibrinogen. *Scand J Work Environ Health* 2002; 28(4): 238-48.

117. Peter R, Alfredsson L, Hammar N, Siegrist J, Theorell T, P. W. High effort, low reward, and cardiovascular risk factors in employed Swedish men and women: baseline results from the WOLF Study. *J Epidemiol Community Health* 1998; 52: 540-7

118. Fransson EI, Nyberg ST, Heikkila K, et al. Comparison of alternative versions of the job demand-control scales in 17 European cohort studies: the IPD-Work consortium. *BMC public health* 2012; 12(1): 62.

119. Nyberg ST, Heikkilä K, Fransson EI, et al. Job strain in relation to body mass index: pooled analysis of 160 000 adults from 13 cohort studies. *J Intern Med* 2012; 272(1): 65-73.

120. Fransson EI, Heikkila K, Nyberg ST, et al. Job Strain as a Risk Factor for Leisure-Time Physical Inactivity: An Individual-Participant Meta-Analysis of Up to 170,000 Men and Women: The IPD-Work Consortium. *Am J Epidemiol* 2012; 176(12): 1078-89.

121. Nyberg ST, Fransson EI, Heikkila K, et al. Job strain and cardiovascular disease risk factors: meta-analysis of individual-participant data from 47,000 men and women. *PloS one* 2013; 8(6): e67323.

122. Nyberg ST, Fransson EI, Heikkila K, et al. Job strain as a risk factor for type 2 diabetes: a pooled analysis of 124,808 men and women. *Diabetes Care* 2014; 37(8): 2268-75.

123. van den Bossche S, Hupkens C, de Ree S, Smulders P. Nationale Enquête Arbeidsomstandigheden 2005: methodologie en globale resultaten. [Netherlands Working Conditions Survey 2005: methodology and overall results]. . Hoofddorp: TNO Work & Employment, 2006.

124. Heikkilä K, Nyberg ST, Fransson EI, et al. Job Strain and Tobacco Smoking: An Individual-Participant Data Meta-Analysis of 166 130 Adults in 15 European Studies. *PloS one* 2012; 7(7): e35463.

125. Heikkilä K, Nyberg ST, Fransson EI, et al. Job Strain and Alcohol Intake: A Collaborative Meta-Analysis of Individual-Participant Data from 140 000 Men and Women. *PloS one* 2012; 7(7): e40101.

126. Matthews KA, Owens JF, Kuller LH, Sutton-Tyrrell K, Lassila HC, Wolfson SK. Stress-induced pulse pressure change predicts women's carotid atherosclerosis. *Stroke* 1998; 29(8): 1525-30.

127. D'Agostino RB, Sr., Vasan RS, Pencina MJ, et al. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. *Circulation* 2008; 117(6): 743-53.

128. Kivimaki M, Hamer M, Batty GD, et al. Antidepressant medication use, weight gain, and risk of type 2 diabetes: a population-based study. *Diabetes Care* 2010; 33(12): 2611-6.

129. Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics* 1977; 33(1): 159-74.

130. Riley RD, Lambert PC, Abo-Zaid G. Meta-analysis of individual participant data: rationale, conduct, and reporting. *BMJ (Clinical research ed* 2010; 340(5): c221.

131. Simmonds MC, Higgins JP, Stewart LA, Tierney JF, Clarke MJ, Thompson SG. Meta-analysis of individual patient data from randomized trials: a review of methods used in practice. *Clinical trials (London, England)* 2005; 2(3): 209-17.

132. Stewart L, Tierney J, Clarke M. Chapter 18: Reviews of individual patient data. In: Higgins J, Green S, eds. Cochrane Handbook for Systematic Reviews of Interventions Version 501 [updated September 2008]: The Cochrane Collaboration; 2008.

133. Altman DG, Egger M, Davey Smith G, eds. Systematic reviews in health care: meta-analysis in context. 2nd ed. London: BMJ Books; 2001.

134. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003; 327(7414): 557-60.

135. Karasek R, Choi B, Ostergren PO, Ferrario M, De Smet P. Testing two methods to create comparable scale scores between the Job Content Questionnaire (JCQ) and JCQ-like questionnaires in the European JACE Study. *Int J Behav Med* 2007; 14(4): 189-201.

136. Kawakami N, Fujigaki Y. Reliability and validity of the Japanese version of Job Content Questionnaire: replication and extension in computer company employees. *Ind Health* 1996; 34(4): 295-306.
137. Niedhammer I. Psychometric properties of the French version of the Karasek Job Content Questionnaire: a study of the scales of decision latitude, psychological demands, social support, and physical demands in the GAZEL cohort. *Int Arch Occup Environ Health* 2002; 75(3): 129-44.
138. Fujishiro K, Lawson CC, Hibert EL, Chavarro JE, Rich-Edwards JW. Job strain and changes in the body mass index among working women: a prospective study. *Int J Obes* 2015; 39(9): 1395-400.
139. Kivimaki M, Singh-Manoux A, Nyberg S, Jokela M, Virtanen M. Job strain and risk of obesity: systematic review and meta-analysis of cohort studies. *Int J Obes* 2015; 39(11): 1597-600.
140. Overgaard D, Gyntelberg F, Heitmann BL. Psychological workload and body weight: is there an association? A review of the literature. *Occup Med (Lond)* 2004; 54(1): 35-41.
141. Siegrist J, Rodel A. Work stress and health risk behavior. *Scand J Work Environ Health* 2006; 32(6): 473-81.
142. Wardle J, Chida Y, Gibson EL, Whitaker KL, Steptoe A. Stress and Adiposity: A Meta-Analysis of Longitudinal Studies. *Obesity (Silver Spring)* 2011; 19(4): 771-8.
143. Lin YP, McCullagh MC, Kao TS, Larson JL. An integrative review: work environment factors associated with physical activity among white-collar workers. *West J Nurs Res* 2014; 36(2): 262-83.
144. Griep RH, Nobre AA, Alves MG, et al. Job strain and unhealthy lifestyle: results from the baseline cohort study, Brazilian Longitudinal Study of Adult Health (ELSA-Brasil). *BMC public health* 2015; 15: 309.
145. Oshio T, Tsutsumi A, Inoue A. The association between job stress and leisure-time physical inactivity adjusted for individual attributes: evidence from a

Japanese occupational cohort survey. *Scand J Work Environ Health* 2016; 42(3): 228-36.

146. Huth C, Thorand B, Baumert J, et al. Job strain as a risk factor for the onset of type 2 diabetes mellitus: findings from the MONICA/KORA Augsburg cohort study. *Psychosomatic medicine* 2014; 76(7): 562-8.

147. Mutambudzi M, Javed Z. Job Strain as a Risk Factor for Incident Diabetes Mellitus in Middle and Older Age U.S. Workers. *J Gerontol B Psychol Sci Soc Sci* 2016.

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